24th Sept 2016

Submission of comments on 'Good Manufacturing Practice for Advanced Therapy Medicinal Products' (EMA/…/…)

Comments from:

| Name of organisation or individual |
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*Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.*

*When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).*

1. General comments

| Stakeholder number  *(To be completed by the Agency)* | General comment (if any) | Outcome (if applicable)  *(To be completed by the Agency)* |
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|  | Cell Medica welcomes the extensive development of this document from the text in the first draft published.  We believe this brings a more appropriate level of flexibility and understanding of the particular difficulties in application of current EU GMP to ATMP’s in particular small scale autologous products. |  |

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1. Specific comments on text

| Line number(s) of the relevant text  *(e.g. Lines 20-23)* | Stakeholder number  *(To be completed by the Agency)* | Comment and rationale; proposed changes  *(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome  *(To be completed by the Agency)* |
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| Line 105-106 |  | More detail should be provided on Senior Management responsibilities to account for recent EU GMP updates. Suggested text has been provided for inclusion in Section 3.1 but could equally be added here. |  |
| Line 273-274 |  | The line ‘*It may be justified to waive the on-going stability program for products with a very short shelf-life.’* Should be clarified to provide guidance as to what is considered a *very short shelf life* (e.g. less than X days, weeks, months etc) |  |
| Line 300-302 |  | This sentence implies that under a risk based approach for manufacturing it would be possible to manufacture in a Grade A zone with a Grade D background. This is a) considered a high risk for an aseptically produced product regardless of controls in place b) this is inconsistent with other text e.g. Line 323 which states a minimum of Grade C background for investigational ATMP’s.  We would recommend this be changed to Grade C. |  |
| Lines 330 |  | Add *Refrigerators* to list OR remove ~~incubators and freezers~~ and replace with *Temperature Controlled Environments* |  |
| Line 344 |  | More detail should be provided on Senior Management responsibilities as per EU GMP recent updates to Chapter 1 and 2 (e.g. Sections 1-5,1.6,2.1 and 2.4)  The following text should be added ;  *Senior management has the ultimate responsibility to ensure an effective Pharmaceutical Quality System is in place, adequately resourced and that roles, responsibilities, and authorities are defined, communicated and implemented throughout the organisation.* |  |
| Lines 353-354 |  | Addition as shown is recommended. ‘*Personnel working in areas where contamination is a hazard should be given specific training on aseptic manufacturing including the basic elements of microbiology’* |  |
| Line 356 |  | There should be additional flexibility to assess operator aseptic technique. Suggest changing  ~~Prior to participating in routine aseptic manufacturing operations, personnel should participate in a successful process simulation test (see Section 9.5.3).~~  *Prior to participating in routine aseptic manufacturing operations, the aseptic technique of personnel should be assessed, for instance by a competency based test or by participate in a successful process simulation test (see Section 9.5.3).* |  |
| Line 396 |  | Replace ~~‘clean (sterilised)’~~, with ‘*sterile clean’*. This could be interpreted that sterilised garments are only optional. |  |
| Line 407-408 |  | Clarify sentence *“When a person moves from one clean room to another clean room appropriate disinfection measures should be applied”*. Is this meant to apply to all cases even if working on similar products or only if personnel have been exposed to live micro-organisms, genetically modified organisms, toxins or animals etc as described in Lines 403-407. Suggest rewording to clarify as  *“If such passage is unavoidable, appropriate control measures (having regard to the risks) should be applied including if a person moves from one clean room to another clean room appropriate disinfection measures should be applied.”* |  |
| Lines 461-462 |  | Comment: The manufacture of other medicinal products can be very similar to ATMP (similar starting materials with just a difference in unit operations or medical indication. A justification to require a dedicated area should not solely be based on product classification. For example, in Germany hematopoietic stem cell preparations are medicinal products; it does not stand to reason why these should be segregated from ATMP manufacture.  Delete sentence, because “conventional” GMPs are applicable to those “other medicinal products” guiding the necessary degree of segregation and dedication.  Proposed change:  ~~If the manufacturing site produces medicinal products other than ATMPs, the manufacture of ATMPs should take place in a dedicated area of the facility.~~  Alternatively clarify that on a risk basis that that the preparation of ATMPs and non-ATMP cell and tissue preparations, or something similar, would be appropriate in the same area. |  |
| 508-511 |  | Regarding special considerations for isolator validation we would add;  *“Isolators should be introduced only after appropriate validation. Validation should take into account all critical factors of isolator technology, for example the quality of the air inside and outside (background) the isolator, sanitisation of the isolator, the impact of sanitising agents on materials sanitised and on the process, the transfer process and the isolator’s integrity”*  Particularly with cell culture work, it is very important that the sanitising agents do not directly impact the materials or are absorbed into materials and then have a negative impact on cell growth and product quality. |  |
| (Line 529), foot note 6 |  | Comment: The phrasing “should be measured after a short clean-up period” for at rest measurement implies that at rest measurements could only be performed after passing through an operational state recently. Retain wording of current Annex 1.  Proposed change:  The particle limits should be ~~measured~~ achieved after a short “clean up period” of approximatively 15-20 minutes after completion of operations. |  |
| Line 540-542 |  | Temperature and humidity should only be routinely monitored if they are relevant to process control. Suggest the sentence is reworded as follows;  *“The environmental monitoring program should include the following parameters: particulate matter/microbiological contamination, air pressure differentials, airflow direction and where appropriate control is required for the process, temperature and relative humidity.”* |  |
| Line 546 |  | It is unclear exactly what is required by the following sentence. “Additionally, monitoring “at rest” should be performed as appropriate in order to identify potential incidents (e.g. prior to the start of manufacturing and post sanitization)”. Should be re-worded to clarify is this is intended as a routine task or as required. |  |
| Line 601 |  | Remove ~~“(Average Values):”~~  There is no accepted standard on how to apply an average (e.g. per session, per week or a longer trend period) and does not make sense from a microbiological trending perspective. |  |
| Line 603 |  | Appropriate alert limits should also be defined. Consider rewording ;  “Appropriate alert and action limits should be defined. If action limits are exceeded, appropriate corrective actions should be taken. These should be documented.” |  |
| Lines 660-661 |  | Comment: Aseptic connections can also be done by closed systems such as sterile tube welding (functionally closed systems) which do not need a grade A in B. Current wording is too categorical.  Proposed change: Add  Aseptic connections can also be made using a functionally closed system such as sterile tube welding. |  |
| Lines 765-766 |  | Comment: Batch Definition, should be changed or removed.  Imagine an autologous bulk product is filled into a series of 10 cryovials and cryopreserved. Why should each unit (cryovial) be considered a distinct batch as they would be manufactured in a single process producing a uniform product ?  Proposed change:  Batch definition. ~~For autologous products, each unit should be considered a distinct batch.~~ A defined quantity of starting material, packaging material or product processed in one process or single series of manufacturing operations (incl. a single series of sterilisation operations) so that it could be expected to be homogeneous.  Alternatively delete lines 765-766. |  |
| Line 786 to 799 |  | This section does not clearly state the expected contents of the Product Specification or it’s purpose (to be a reference source for the QP to release against. An adaption of the current text in EU GMP, Section 9 of Annex 13 is recommended. |  |
| Line 861 to 863 |  | This sentence states that a Site Master File is required for every site involved in authorised ATMP’s. Does this mean that SMF is not required for sites only manufacturing investigational ATMP’s? It may be clearer to state that this is the case. It is currently expected that an SMF is prepared for all site license applications for IMP’s and prior to inspections. |  |
| (Line 929), foot note 14 |  | Comment: 2.6.12 is on bioburden – not sterility  Proposed change:  Ph.Eur. chapter 2.6.1~~2~~ on sterility testing describes the use of neutralising substances for products containing antibiotics. |  |
| Lines 957 |  | Comment: It would be helpful to clarify expectations on identity testing.  Proposed change: Add  For raw materials and excipients authorised as medicinal products or bearing a medical device CE-mark identity testing is not be required. |  |
| Line 1205 |  | Comment: The urge to use gasses compliant with EP will in some cases increase costs unnecessarily. Higher (than EP) technical grades are often available but come without a costly batch specific certificate (so not EP grade). EP-grade gas should not be required for CO2-incubators.  Proposed change:  Where ~~possible~~ supported by documented risk assessment, gasses of technical grades can be used instead of those compliant with the European Pharmacopoeia ~~should~~ can be used. |  |
| Lines 1271-1274 |  | Comment: The meaning of the sentence “Likewise …” is not clear, in particular the phrase “provided that there is separated expulsion of the exhausted air”. Does this mean isolator and/or biological safety cabinets must have 100% of their air exhausted out of the room and facility with no air recirculated?  It is proposed that this risk would this be mitigated if the exhaust air were double or triple filtered?  This section could benefit by re-wording to make it clear what activities can be conducted in the same room. |  |
| Lines 1296-1297 |  | Comment: Most sterilised (single use) items are not available on the market with a number of wrappings commensurate with the number of stages (that may be 3-4 until they get into grade A). This is too strict a requirement.  Proposed change:  Sterilisation of articles and materials elsewhere is acceptable provided that there are multiple wrappings, if possible as appropriate to the number of stages of entry to the clean area,… |  |
| Line 1298 |  | As a high proportion of materials for ATMP manufacturing (single use) cannot be sterilised through a double ended steriliser, they will be manually surface sanitised. It may be of benefit to provide guidance as to expectations for this process e.g. if a manual process, the number of sanitisation steps, use of sporicides?, technique (spray **and** wipe) etc. |  |
| Lines 1354 and 1356 |  | It is not clear how to apply the concept of process simulation *per shift* for small scale highly manual operations e.g. preparation of autologous products, which may occur in multiple rooms.  There should be a requirement to re-qualify personnel involved in aseptic production by means of a competency based aseptic technique test and/or participation in a process simulation test. |  |
| Lines 1459-1461 |  | Comment: ISO 14644-2:2015 states that re-qualification should be performed annually and does not explicitly require grade A classification every six months. Reference to this standard should be sufficient and conflicting messages avoided. In case of “very small production” (meaning low frequency?) there is a lack of frequent data which is not supportive of a lower classification frequency.  Proposed change: Delete  ~~In general, for clean rooms of grade A, requalification is expected every six months, while for B, C and D grades requalification is expected on a yearly basis. A different frequency may, however, be justified in case of very small production.~~ |  |
| Lines 1490-1493 |  | Comment: That some tests should be performed at the vendor’s site is too strict a requirement.  Proposed change:  … and some tests ~~should~~ could be performed at the vendor’s site … |  |
| Lines 1639-1640 |  | Comment: “validated throughout clinical development” would mean validated even in/for phase I clinical trial, which is not consistent with “… finalized before phase III …”  Proposed change:  Potency assays should be qualified in ~~validated throughout~~ early clinical development and (i.e. typically validation finalized before phase III clinical trials). |  |
| Lines 1659-1661 |  | Comment: Requirements for QP’s qualification other than those laid down in Directive 2001/83/EC will raise debate how this should be demonstrated, especially as “training and experience” are not differentiated. The wording should state  “training and/or experience”.  It is unclear if these will be additional requirement or alternative to those required in Directive 2001/83/EC. We agree a slightly different set of skills are required to act as a QP for ATMP’s and the emphasis should be on those described in Lines 1660-1661 rather than many of the current requirement e.g. organic chemistry and applied physics.  Is Annex 16 replaced altogether for ATMPs? |  |
| Lines 1882-1888 |  | Comment: Retaining Reference samples of critical raw materials should be recommended but not considered mandatory (short shelf life, minute quantities, considerable costs – to name just a few potential reasons).  Proposed change:  Reference samples of critical raw materials (e.g. cytokines, growth factors) are ~~important~~ recommended to investigate possible quality problems with the product. The assessment whether to retain a specific raw material~~s~~ is ~~critical~~ beneficial for root cause analysis should be done by the manufacturer having regard to the specific risks and possible mitigation measures (e.g. increased QC controls). |  |
| Lines 1923-1924 |  | Comment: In our opinion, a cryopreserved sample is not adequate for sterility controls |  |
| Line 1937 |  | Proposed change:  ~~critically~~ criticality |  |
| Line 1972 to 1977 |  | It should be recognised that for autologous products the ongoing stability monitoring may be difficult and alternative starting materials may need to be used. It may not be ethical to procure starting material in sufficient quantities from patients purely for an ongoing stability testing program. |  |
| Lines 2018-2019 |  | Comment: “… reference samples should be kept by, or made available to, the contract giver”  This is not realistic as the contract acceptor might be a licensed establishment and needs to keep the samples within their premises. Same to original documentation. |  |
| Line 2089 |  | It is unclear how “Cell recovery after cryo-storage” differs from those activities listed in 2085-2087.  Suggest to delete line  ~~“Cell recovery after cryo-storage”~~ |  |
| Lines 2104 to 2113 |  | This section should be expanded to describe the situation for investigational ATMPS. The responsibility for describing the method of administration is typically performed by the Sponsor and not the manufacturer (who may be a Contract Manufacturer). For investigational ATMP’s this process need not be validated but assessed or qualified to ensure it can be administered without negative impact to product safety. |  |
| Lines 2140-2141 |  | Comment: For equipment the term “qualification” should be applied, in line with Section 10.1.  Proposed change:  ~~Validation~~ Qualification of the equipment: The ~~validation~~ qualification process as described in Section 10.1 2140 applies. |  |