22/09/2016

Submission of comments on 'Good Manufacturing Practice for Advanced Therapy Medicinal Products'

Comments from:

| Name of organisation or individual |
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| Bundesverband der Pharmazeutischen Industrie (BPI e. V.) – German Pharmaceutical Industry Association |

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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)* |
| --- | --- | --- |
|  | BPI represents the majority of Germany’s industry in the field of cell-based Advanced Therapy Medicinal Products (ATMP), nearly all of these companies being SMEs. Therefore, the comments of BPI represent the voice of SMEs that are especially invited to comment by the Commission.  BPI highly welcomes the proposals made in the consultation guidelines which in our opinion pave the way for feasible ATMP development in Europe leading to increased availability of these products without making compromise to quality and safety of the products.  The role of the sponsor should be defined more in detail. In clinical trials currently a lot of ATIMPs will be manufactured by CMOs for a sponsor independent from the CMO. Typically all issues within the clinic are in the responsibility of the sponsor and a CMO has no relationships with the clinic. Within the document there is more or less only the wording “manufacturer” but the manufacturer isn’t the sponsor in a lot of cases! This should be reflected.  General suggestions:   * more consideration on implication of GTMPs with respect to environment and decontamination since there will be no other “GMP for GTMP”); * the intra-document-referencing is not very well (see contradictions mentioned above; * the inter-document-referencing between published documents isn’t well either. |  |

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)* |
| --- | --- | --- | --- |
| 128-130 |  | Comment:  It should be clarified that current other guidelines (e.g. EU-GMP) will no longer apply to ATMPs or at least have to be considered together with GMP for ATMP Document. We strongly recommend cross-referencing to this consultation document where applicable. |  |
| 151 f. |  | *“…and allogenic products in a donor matched scenario:”*  Comment:  Allogenic products are not always donor matched. Therefore this should also apply to HLA-mismatched settings, which is a common clinical situation or not applicable in certain settings or for certain products. |  |
| 268-272 |  | Comment:  A particular matter test isn’t applicable for cell suspensions. Also detecting foreign visible particles is more a theoretical exercise in a dense cells suspension. The only meaningful test is appearance (colour etc.).  Proposed change (if any):  Deleting this paragraph. |  |
| 429-434 |  | Comment:  It should also be included that Head of Manufacturing / or Head of Quality Control can perform in personal union also the QP function.  Proposed change (if any):  Adding of such an additional sentence that reflects this issue. |  |
| 461-471 |  | Comment:  For clarification please add that each closed system is to be regarded as an area (as referred to in line 1268). |  |
| 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.~~ |  |
| 462 |  | Comment:  It should be clarified that if ATMPs and non-AMTPs are manufactured in separate closed systems, then they can be manufactured in the same facility (see comment to line 461 above) because closed system should be considered as physical segregation. |  |
| 481-483 |  | Comment:  It should be clarified that „contaminated materials“ are e.g. patient material or waste material (definition of “contaminated materials”). |  |
| 506-507 |  | Comment:  This statement is supported strongly. |  |
| 516-519 |  | Comment:  contradiction to line 322 |  |
| (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. |  |
| 546 |  | Comment:  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)”. |  |
| 561-568 |  | Comment:  It should be clearly written that particle monitoring in class B clean rooms need not be performed for the full duration of critical processing (only for grade A).  Proposed change (if any):  Adding an additional sentence that reflects this issue. |  |
| 659 f. |  | Comment: *„The location and installation of the equipment should be adequate to minimize risks of errors or contamination. Aseptic connections should be performed in a critical clean area of grade A with a background clean area of grade B.“*  For first in man trials it is accepted to make connections in an A in C area (line 322 f.), which contradicts the statement above.  Proposed change (if any):  Thus, we suggest to add the same sentence to the statement in lines 659 f. as well in order to harmonize the requirements. |  |
| 660-661 |  | Comment: Aseptic connections can also be done by 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. |  |
| 765-766 |  | Comment: 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?  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. |  |
| 798 |  | Comment:  What is meant with “manufacturing order”?  Proposed change (if any):  Clarification of this wording. |  |
| 865-870 |  | Comment: The shorter time lines mentioned in 6.5. are from the practical standpoint in conflict to the data mentioned in 6.6. (to the 30 years). Most of the issues mentioned in 6.6 (line 889-909) are more or less part of a typical batch record/are integrated into the batch record. Writing “Batch documentation (i.e. documents in the batch processing record……) should be kept for one year after expiry of the batch or at least five years after certification……” isn’t really practically and is quite confusing. It’s impossible to look after 1 or 5 years into the huge amount of bulky batch records of autologous products and divide into issues that are important for traceability (and must be archived further) and into issues that can be destroyed.  Proposed change (if any):  Clarification in regard to the time lines. If possible harmonization. |  |
| (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 product or bearing a medical device CE-mark identity testing is not required. |  |
| 1030-1036 |  | Comment:  It’s not realistic that initial processing steps “are manufacturing activities that should be conducted in accordance with the manufacturing requirements for pharmaceuticals”. In many cases such steps are performed in the clinic, e.g. within an operating theatre. It’s not realistic to apply GMP to such activities.  Proposed change (if any):  Requirements for pharmaceuticals should only apply in case of substantial manipulation of the starting material. |  |
| 1172 |  | Comment:  “Where necessary” should be further explained.  Proposed change (if any):  Explaining, e.g. by using an example? |  |
| 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 be used. |  |
| 1205 |  | Comment:  Liquid nitrogen for storage of cells in the vapor-phase of liquid N2 should be excluded from this section.  Proposed change (if any):  Writing “9.3.2. isn’t applicable for liquid nitrogen for storage of cells in closed containers in or above liquid nitrogen. |  |
| 1227-1229 and f. |  | Commment:  We would like to propose additional definitions with regard to aseptic connections (e.g. needles in septum, luer locks), sterile connections (e.g. tube to tube welding, aseptic connections with a sterile septum and spikes with filters). |  |
| 1267-1274 |  | Comment:  The described separation in place isn’t viable for large scale commercial production of complex ATMPs for the market after EMA approval. Very complex ATMPs like CAR T, DC’s etc. are difficult to manufacture within a closed and rigid system like an isolator (space restrictions within such an isolator, too many materials that must be transferred into the grade A area, several grade A activities per manufacturing day etc.). For such kind of products an appropriate sized BSC with laminar flow is the class A environment of choice. To have only one BSC in one class B room means for commercial large scale production of a complex ATMP hundreds of class B rooms with all the associated space consuming infrastructure for entering the rooms (corridors, airlocks etc.). That’s not practical. Therefore it should be allowed to have more than one BSC within a larger grade B room if some preconditions are given (e.g. a kind of segregation in separated working areas for each batch with dedicated devices etc., same kind of (autologous) products [same process] per room etc.). Such a structure is common practice, e.g. in USA but also in Europe there are facilities with more than one BSC per room.  Proposed change (if any):  Including this possibility and mentioning of the preconditions that must be fulfilled. |  |
| 1268 f. |  | Comment:  We would like to clarify that the term „closed system“ still applies if: spiking of buffers is an aseptic process if the buffer is sterile filtered before reaching the closed system by the use of micro-organism retentive filters. |  |
| 1270 |  | 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? Would this be mitigated if the exhaust air is double or triple filtered?    Proposed change (if any):  This section could benefit by re-wording to make it very clear what activities can be conducted in the same room. |  |
| 1296-1297 |  | Comment: Many 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,… |  |
| 1326-1328 |  | Comment:  A filter integrity testing isn’t applicable for typically used sterile filters units in cell culture (e.g. the typically used filter bottles or small filters for syringes). The standard devices used for filter integrity testing (e.g. Sartocheck®) can’t be used for such kind of filters.  Proposed change (if any):  Please define exemptions. |  |
| 1331 |  | Comment:  Within 9.5.3 “Aseptic process validation” it is not clearly distinguished between “aseptic operator qualification” for each single clean room operator for an ATMP process and the performance of media fill process validations with the goal to qualify the manufacturing process itself + the used rooms / equipment.  Proposed change (if any):  Including a paragraph that deals with the topic aseptic operator qualification for operators involved in aseptic manufacturing of ATMPs. E.g. guidance in regard to frequency (e.g. 3x as initial qualification, 1 repetition per year), content (e.g. matrix approach that includes only critical open or semi-closed steps). |  |
| 1339-1345 |  | Comment:  Complex ATMP manufacturing processes contain a lot of repetitions of the same manufacturing steps (e.g. spiking of a certain type of bag, connecting the same type of vessels, centrifugation of a constant volume in the same kind of centrifuge vessel, using the same sterile washing kit……). Repeating these uniform steps during a Media Fill again and again isn’t an added value, especially for steps that are not really open steps, but more semi-closed (like spiking, welding etc.). Therefore each equal step should be performed only one time within a media fill procedure.  Proposed change (if any):  Including of a sentence that equal steps must not be repeated and can be performed only one time within the whole Media Fill procedure. This should be justified by a risk analysis. Only clear open steps or very risky steps should be repeated. |  |
| 1353-1354 |  | Comment:  The formulation “…tests per shift” isn’t really clear for an ATMP manufacturing process that typically covers several manufacturing days per batch with very different length/different activities per manufacturing day. What does “per shift” mean (only one time per six month in case that the manufacturing is performed in a one shift system, e.g. only in normal day shift)?  Proposed change (if any):  The phrase …“tests per shift” should be explained more clearly. |  |
| 1355 |  | Comment:  Every six month is too tight. A yearly repetition is sufficient if there are no changes of process, rooms etc and if the process contains only a limited amount of open steps.  Proposed change (if any):  Changing to every 12 month. |  |
| 1356 |  | Comment:  The formulation “….per shift” isn’t really clear for an ATMP manufacturing process that typically covers several manufacturing days per batch with different length/different activities per manufacturing day. What does “per shift” mean (only one time per six month in case that the manufacturing is performed in a one shift system, e.g. only in normal day shift)?  Proposed change (if any):  The phrase …“per shift” should be explained more clearly. |  |
| 1459-1460 |  | Comment:  It should be distinguished between grade A clean rooms and other grade A areas (BSC, isolator). It should be included that for BSCs a full requalification (all issues according to DIN EN 12469) should be performed only every 12 months and not every 6 months. The manufacturers of BSC’s recommend the procedure according to DIN EN 12469 one time per year.  Proposed change (if any):  Inclusion of a sentence that a full procedure according DIN EN 12469 isn’t necessary every 6 month. |  |
| 1459-1461 |  | Comment: ISO 14644-2:2015 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.~~ |  |
| 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 … |  |
| 1575 |  | Comment:  The wording “consecutive” should be deleted for autologous products. In case of autologous products and in case of using patient-derived starting material it’s realistic that a batch can fail (due to intrinsic factors related to the starting material).  Proposed change (if any):  Deleting “consecutive” or writing “in best case consecutive”. |  |
| 1624 |  | Comment:  Validation of the manufacturing process for investigational ATMP is not necessary. Contradictory to the requirements to get a manufacturing license where validation is necessary in general. |  |
| 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~~)~~. |  |
| 1659-1661 |  | Comment: Requirements for QP’s qualification should be reworded. Training leads to experience and Article 49 of Directive 2001/83 is focussing on experience.  Proposed change:  In addition to having the qualification requirements provided under Article 49 of Directive 2011/83, QP´s responsible for ATMPs should have ~~training and~~ experience relevant to specific characteristics of these products, ~~including~~ as appropriate cell and tissue biology, … |  |
| 1761-1763 |  | Comment:  Should be harmonized with the 30 years necessary for the issues mentioned in 6.6. It’s not practically to discard parts of the batch documentation earlier than other parts.  Proposed change (if any):  Harmonization with the wording in 6.5. and 6.6. |  |
| 1808 |  | Comment:  Could the regulators please give advice on how the QP is responsible: are those kind of “out-of-spec products” obliged QP-release before administration or are the doctors solely responsible and no QP-release is needed?  Proposed change (if any): if physician wants to administer, the product has to be always QP-released. A strong QP-Doctor-interaction is necessary to assess the risk/impact of the specific OOS-result. |  |
| 1816-1817 |  | Comment:  This requires an established system by the authorities so more clarification on notification process is needed. |  |
| 1817 |  | Comment:  A time point for such notification should be mentioned (e.g. “in front of administration of the drug product”).  Proposed change (if any):  Clarification of the time point. |  |
| 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). |  |
| 1887-1888 |  | Comment:  The wording …“retained for two years after the batch release or one year after expiry date of the relevant batch, whichever is the longest.” is difficult to realize due to the fact that in autologous setting raw materials are used very often for a bigger amount of individual patient batches over a longer period of time. It’s hard to track time-wise. In addition to that the raw materials are often expired in front of the expiry date of the manufactured ATMP batches – what kind of meaningful analyses can be realistically done from an expired raw material?  Proposed change (if any):  Defining a time point that is related to the expiry date of the raw material itself? |  |
| 1891 |  | Comment:  It’s a reference sample and not a retention sample.  Proposed change (if any):  Change wording. |  |
| 1900 |  | Comment:  It’s a reference sample and not a retention sample.  Proposed change (if any):  Change wording. |  |
| Lines 1923-1924 |  | Comment: In our opinion, a cryopreserved sample is not adequate for sterility controls |  |
| Line 1937 |  | Proposed change:  ~~critically~~ criticality |  |
| 1971 |  | Comment:  Not in all cases it will be possible to use patient derived batches for stability programs, e.g. in case of small batch size in the autologous setting. Therefore the potential use of material derived from healthy volunteers should be mentioned.  Proposed change (if any):  Inclusion of a sentence that mentions the possibility to use starting material from healthy volunteers in special cases (e.g. small batch size). |  |
| 1992 |  | Comment:  The wording “routinely” should be included in front of “outsourcing”.  Proposed change (if any):  Changing into “Activities that are routinely outsourced….”. |  |
| 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. |  |
| 2081 |  | Comment:  What is a substantial manipulation? Regulation (EC) 1394/2007 Annex 1 defines only non-substantial manipulations. At least there should be a cross-reference to Regulation (EC) 1394/2007 regarding manipulation definitions. |  |
| 2089 |  | Cell recovery after cryo-storage ?? |  |
| 2102 |  | Comment:  The special situation during clinical trials should be evaluated in regard to 16.2. In clinical trials a lot of ATIMPs will be manufactured by CMO’s for a sponsor independent from the CMO. Typically all issues within the clinic are in the responsibility of the sponsor and a CMO has no relationships with the clinic. This should be reflected.  Proposed change (if any):  Introduction of the sponsors’ role in regard to the responsibility for issues performed in the clinic. |  |
| 2109 |  | Comment:  The wording “The manufacturer should document the reconstitution process” sounds misleading. The documentation is performed by the clinic (e.g. with documents provided by the manufacturer). Does it mean that the documentation should be sent after performance to the manufacturer for integration in the batch record and archiving?  Proposed change (if any):  Clarification of this issue. |  |
| 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. |  |
| 2160-2162 |  | Comment:  The responsibility of the maintenance program must be driven by the ATMP manufacturer. The device manufacturer should provide a maintenance scheme (timelines, content) to guarantee device warranty. |  |
| 2176 f. |  | Comment:  *“controlled but non-classified background environment acceptable for short processes (while patient waiting)”*  This paragraph doesn’t consider longer procedures while patient might be even waiting at home - why limit to short processes while patient is in surgery? A validated closed system is proven for having no contact between the product and the environment, even reduced particle monitoring is acceptable if justified (refer to lines 572 f.), so if the patient can wait days during manufacture, so longer procedures performed under validated closed system should also be manufacturer controlled non classified room for weeks. |  |
| 2200 (end of the line) |  | Comment:  number of the section to refer to is missing! |  |
| 2202-2203 |  | Comment:  Same QP can be responsible for more than one site for the release of the product. Need more precision: is there still the need of a QP per manufacturing site? Can the “central” release of the multi-site-QP take place on its own or the local release by the local QP needed first? |  |

Please add more rows if needed.