



Responses from the ATMP Manufacturing Community (amc) to the Public Consultation Paper on Good Manufacturing Practice for Advanced Therapy Medicinal Products pursuant to Article 5 of Regulation 1394/2007

The amc is an association of Stakeholders manufacturing ATMPs in the UK and neighbouring countries (e.g. Ireland and The Netherlands). Its over 170 members include a mixture of industry and health professionals, approximately 20% of which come from SMEs. Further details are available on the amc website.

<http://www.atmpmanufacture.org/Home/Home.php>

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General comments (two responders with similar comments):

1) The majority of the consultation paper has been reviewed as a draft Annex to EudraLex Volume 4 (the GMP Guide). The Commission's attempt to draft such an Annex is welcomed, but it is requested that all other applicable guidance in existing Annexes is neither duplicated nor contradicted in an ATMP-specific Annex, as this would lead to inevitable confusion and conflicting guidance. For example, Annexes 1 and 2 relating to aseptic production of biologicals products are very relevant to much of ATMP production. Also, Annex 13 guidance for IMPs should be cross referenced instead of providing conflicting guidance, e.g. relating to manufacturing and quality control validation, and the provision of reference and retention samples.

2) In general, we feel that it is neither needed nor useful to have GMP guidelines specific for ATMP's. The current document bears the risk of implementing a 'GMP-light' system related to the production and quality assurance of ATMP's which we feel would not be beneficial.

The majority of the standards listed can already be found in existing guidance. Rewriting existing GMP principles into a dedicated GMP for ATMPs will result in the generation of conflicting guidance and should be avoided. Having different regulations for different types of drugs is highly likely to do nothing to improve clarity on regulatory issues that are already open to interpretation.

It is true however that the specifics of development and production of ATMP's bring challenges to the manufacturing and control thereof. We do not believe that an adaptation of the GMP guidelines specifically for ATMP's will be instrumental to the field in the long run.

The acceptance of ATMP's as routine medicinal products will only be possible when known, existing and stringent rules for quality and safety are applied as they are defined now in Eudralex Vol 4 and related documents.

Moreover, current and past experience has shown that this is possible. For example, the general principles of GMP have been applied successfully to the production of biologics just as well, while this was also felt to be not possible at first.

The recently introduced redraft of Annex 2 (2013) indicates this principle really well. Annex 2 was a redraft of an existing annex where many of the future guiding regulatory principles for the manufacture of cell based ATMPs have been incorporated taking into account risk based decision making and alongside reference to the existing appropriate guidance.

We feel that in order to facilitate clinical and commercial production of ATMP's the field would much more benefit from a document in which the current, existing GMP rules are translated to practical examples on production and quality control.

Since the pharmaceutical industry as a whole seems to move towards development of complex treatment modalities for smaller indications, such examples could (should) be beneficial for the pharmaceutical industry as a whole. Such document would ideally refer to existing GMP guidelines, and the sections where the examples provided relate to. In the current document, such references are absent.

In the current document, it is often not made clear where standard procedures from Eudralex Volume 4 are described and where specific requirements for ATMPs are given. We would recommend that any reference to standard regulations is specifically cited and any references to new and specific ATMP requirements are made.

Question number	lines	Response
1	97-101	With specific reference to points bracketed at lines 97-101: There could be an argument for the development of 'derogations' in the terms of GMP and MA or CTA to take into account the inherent variability of some autologous ATMPs especially during the early stages of development : i.e. first-in-man and early phase II. Although: it is the opinion of the responder that it would be preferable for competent authorities to acknowledge that variability in the acceptance of wider acceptance criteria for specifications from starting materials all the way through to drug product rather than introduce a principle of 'derogations'.
2	N/A	It is useful to add additional level of detail regarding the application of the risk-based approach. Although as commented above, many of the statements listed below under section 2.1 are already incorporated into the existing GMP guidance and so should not be duplicated in additional guidance but clearly referred to. In fact this statement could be applied across the entire GMP guide, were it is recommended to 'take a risk based approach' but there is no guidance or examples of how this statement should be implemented. Recommendations to what kind of risk analyses would be needed if useful, i.e.: -Aseptic manipulations, specifically; -The number of open handlings in process -The number of open handlings in harvest, formulation and filling -The filling strategy and number of vials -Evaluation of high risk for contamination, both in type of materials used

		<p>as well as handlings</p> <ul style="list-style-type: none"> -Microbial risks to product & environment -Manufacturing procedure, critical process step evaluation -Variability of starting material and its impact on the drug product -Release procedure (in case of short shelf life) <p>Process simulation tests: the existing guidance for PSTs does not fit into the model of autologous & small batch ATMPs.</p>
3	N/A	<p>There are two responses:</p> <p>1) Care should be taken when adopting JACIE standards for tissues and cells that are used non-homologously, because they extend beyond the requirements for procurement, donor testing and preparation as set out in the Directive 2004/23 and its technical directives. Also, JACIE is limited to haematopoietic cells, and cannot be adopted for other cell and tissue types. It is preferable to rely on processes authorised by Member State Competent Authorities appointed under the Directive.</p> <p>Such authorisations may be appropriate for such ATMPs only if the manipulations are not substantial (as defined in Regulation 1394/2007 Article 2 (c)), and if they are identical to those authorised for processing of tissues and / or cells for homologous administration.</p> <p>2) In case of non-homologous used of cells where no substantial manipulation is needed, the minimal requirements of the process should guarantee safety of the product for the recipient, i.e., aseptic handling in a compliant manner with the appropriate testing of the product and cleaning and EM monitoring of the workplace but all of this should be covered under the GMP PQS.</p> <p>Experience shows that it can cause regulatory and compliance confusion, contradictions & unnecessary duplication of compliance activities where alternative or different quality systems are required to be applied. JACIE is not an appropriate accreditation system for ATMPs.</p>
3	121-122	<p>It is stated “for early phases of clinical trials” - please provide more specific guidance, and state Phase I only or Phase I , II and III etc.</p> <p>Please take care not to contradict guidance in Annex 13.</p>
4	N/A	<p>In general the requirements laid out in section 3 are sufficiently well adapted and are covered adequately by existing guidance.</p> <p>In addition, reference should be made to the fact that most ATMP facilities are multi-product and personnel should be specifically trained in avoiding cross contamination and mix-up.</p>
4	147-151	<p>For GMO & Non GMO ATMPs this does not take into account the ability to use closed processing or allow for a risk based approach decision making. If it is closed processing then personnel can move between GMO and non GMO ATMP processes & these could be in the same room.</p>
4	152-154	<p>The QP should be proposed by the MIA or MIA(IMP) licence holder, with the approval of senior management. The appointment of the QP is made only by the Member State Competent Authority, by approval of the personnel at the site(s) following confirmation of the QPs suitability to</p>

		meet the requirements of the relevant EU Council Directives, e.g. formal qualifications and practical experience, as described in the QP Code of Practice. The guidance in these lines of the consultation paper contradicts this appointment procedure, and provides guidance that the MIA or MIA(IMP) licence holder can override the decision of the Competent Authority.
5	N/A	In response to section 4.2: A more detailed description of separated manufacturing areas is beneficial: - Guidance in requirements of cleaning, line clearance and change-over procedure between batches - Guidance to what is allowed regarding manufacturing of multiple batches/products per room / per facility and how regulators expect a risk assessment for this to be performed - Guidance to what is allowed regarding incubation of multiple batches in one incubator / incubators in one room and how regulators expect a risk assessment for this to be performed.
5	188	Manufacture in a multi-product facility <i>is</i> (not maybe) acceptable.
5	192	Comments to prevention of cross-contamination: “or implementation of adequate cleaning and decontamination procedures including the heating, ventilation and air condition systems”: Cleaning between batches of heating, ventilation and air conditions is too stringent. All open handlings are performed in class A area, which is a secured area in a background of Class B. In the event of a spilling, the design of the class A area as well as the Class B room it is in will prevent contamination of the HVAC system due to the fact that air should be single pass and outlet air should pass a HEPA filter. If this requirement would put in place, all ATMP manufacturers would have to change to campaign based production per individual batch and perform VHP between each batch production. From a capacity and business perspective, this is unfeasible. For closed handlings, decontamination of air condition systems is not relevant.
5	212-215	Regardless of the ability to terminal sterilise or not ‘Particular attention should be paid to the filling process’. Premises should be fully ‘QUALIFIED’ regardless of clinical or commercial manufacture
5	218	“Checks to detect the presence of specific microorganisms in the environment (e.g. host organism, yeast, moulds, anaerobes, etc.) should be performed where appropriate.” The risk to maintenance of the aseptic environment is in many cases higher compared to that of standard pharmaceutical products (related to ‘open’ aseptic processing and short shelf life products of manufacturing ATMPs). For that reason, defined guidance of the following is recommended: - Recommendations of impact to release of product in cases where microbiological limits are exceeded during formulation & filling (Vol 4, Annex 1), e.g. >1 CFU observed under class A versus no growth of micro-organisms in sterility test of final product - Guidance in requirements for EM trending data, minimal

		corrective measurements were excursions in EM microbiological testing results within facility/rooms/operation.
6	N/A	It is preferable to allow several incubators in a cleanroom, which are dedicated for a product (with different lots / patients inside) while working on another project in the same cleanroom.
7	231-233	<p>There were two independent comments from our members relating to this section, and a third similar comment regarding Question 8 below.</p> <p>1) There has been an increase in the adoption of closed systems for aseptic manufacture of ATMPs. Such validated systems minimise the risks of contamination far greater than open systems conducted in Grade A with a Grade B background, even when conducted in Grade D clean rooms. Hence, it would be a grave error to ignore this innovation in GMP guidance with a general statement that Grade A with a Grade B background is required for pivotal clinical trials and commercial production.</p> <p>2) Grade A with Grade B background should be always required when working under Laminar Air Flow. For working with other Grade backgrounds (C or D), technical solutions are now available that ensure maximum protection of the product during aseptic processes, as for instance Closed-RABS or Isolators.</p>
8	N/A	<p>Two separate responders have made comments:</p> <p>1) The use of validated closed systems should be permitted in Grade D zones, including those for the production of Gene Therapies. Areas where open processing occurs in such areas should be limited to validated isolators with appropriate containment.</p> <p>2) Where processing is 'semi-open': Consideration could be given the move to a grade C background with an A working zone for aseptic manipulations (as currently recommended for cell banking for biologicals) based on a risk based approach and with appropriate controls whether it be for early phase clinical work or marketed products. Current practices for many cell therapy based ATMPs do not easily fit into the concept of a grade B clean room (for example the requirement to centrifuge cells or even dissection whole organs). Where these activities are followed by incubation in closed flasks, bags or fermenters, incubation in a grade C background should be acceptable. However for truly 'open processes' the following applies:</p> <p>For any 'open' aseptic handling, the use of clean rooms with an A grade working area in a background B grade must be maintained, especially for early phase clinical trials. During these early phase clinical trials, the process probably has:</p> <ul style="list-style-type: none"> - The highest level of open handlings - The lowest defined control strategy and testing of the ATMP product - No or limited validation of QC testing - Highest likelihood of patients that have gone through a series of

		<p>previous treatments and as a result to that are more prone to infections</p> <p>-</p> <p>This needs to be much clearer about the difference between open and closed processing. Open processing is A with B background. A C background should not be acceptable. Closed processing is acceptable in a Grade D background. The use of glove box isolators (Grade A) is acceptable with a D background. This should be the case for all ATMPs including gene therapies. Many facilities are licensed and manufacturing on this basis. Refer to existing Annex 1 and/or 2</p>
10	342-344	<p>Some raw materials of biological origin that are in use in ATMP production are marketed products, for example human serum albumin and recombinant proteins. For such raw materials it is not necessary to mandate contracts and documented quality requirements agreed with third party suppliers.</p>
10	423	<p>Please provide detailed guidance for process and analytical method qualification and validation. We need to know at which stage of the investigational programme this must be the case. Is process validation necessary from Phase III onwards? Is method validation required from Phase III (IIb) onwards? What is the difference between validation and qualification of a method; is qualification following the ICH Q2 without robustness or less?</p>
13	444-445	<p>The guidance provided in this section is outside the scope of GMP. Procurement of starting materials from donors of tissues and / or cells falls under the legislative framework for tissue establishments, as set out in Directive 2004/23 and its technical directives. Guidance relating to the avoidance of contamination and minimal variability for starting materials procured at tissue establishments should be provided by Member State Competent Authorities appointed under Directive 2004/23.</p>
13	466-469	<p>ATMP manufacturers may wish to audit raw material suppliers that are either Blood Establishments or Tissue Establishments. Guidance that this is not necessary may be used by such establishments to refuse entry to ATMP manufacturers auditors. Therefore, please add to the guidance that audits of blood and tissue establishments should be conducted by ATMP manufacturers if it is their choice.</p>
15	575	<p>For clinical trial ATMPs it should remain the case that critical operational and other input parameters remain 'in-development' with an expectation that these would be identified/validated/qualified for a marketed product. Since for many ATMP's (especially those that are cell based) the exact MoA is unclear, it would be instrumental to get input on the minimal amount of knowledge regulators expect when defining critical process parameters and quality attributes. To date, practice is to give a justification based on scientific evidence. However, since specifically in cell therapies animal studies are not always possible or representative, the body of evidence is often limited. Guidance documentation is required for the level of data expected for early phase studies and how this increases towards commercial manufacturing? But the principles for GMP compliance as listed are covered adequately by existing regulation</p> <p>For example: To what extent is the size of the potential patient population of influence to this requirement? Do manufacturing processes need to be qualified on patient material or is healthy donor</p>

		material allowed even when it is commonly known that the results between such starting materials may well differ? Can results from early phase clinical productions be used to complete the validation package for pivotal and commercial production, even when changes to the manufacturing process are made in between?
15	648	It is recommended to provide guidance on the cleaning validation specifically for ATMPs. Vol 4 Annex 15 describes the requirement for cleaning validation but is focused on the efficacy of removal of cleaning agent residuals. For ATMPs, re-use equipment and surfaces in direct contact with cells is rare, and therefore these requirements are less relevant. Disposable materials are used and discarded after usage. Therefore, because of the nature of ATMPs (open handlings, usage of same areas for multiple batches / products in a shorter timeframe) the effectiveness of clean surfaces is more focused on maintaining an aseptic environment. Guidance in effectiveness of aseptic environment in the cleaning strategy would be preferred.
15	682-683	ATMP's should be suitably packaged to maintain quality <u>and asepsis</u> of the product during storage (<u>including during storage at very low temperatures</u>), handling and shipping.
16	711-712	We have similar comments for this section as those for line 423: Please provide guidance regarding the stage in the product life-cycle at which point process validation should be complete.
17	N/A	We provide responses from two reviewers: 1) We recommend that manufacturers adopt the methods of Quality Risk Management (ICH Q9) as far as possible to identify those Critical Process Parameters that have the most impact on the Critical Quality Attributes of ATMPs. These attributes should be reviewed regularly to identify the level of control in batch-to-batch variability, using Product Quality Review procedures (ICH Q10). 2) Process validation of the aseptic processing steps must be carried out but a pragmatic approach to validation of manufacturing must be adopted especially recognising the inherent variability of the biological starting materials and limited supply.
18	N/A	QP certification issues arise where steps, currently considered to be manufacturing, are by necessity carried out outside of the control of the manufacturer. For example, removal of DMSO and re-formulation into a patient dose directly prior to use. For many cell therapy ATMPs these steps currently happen within the patient environment (i.e. hospital) but are clearly outside the control of the manufacturer's QP. Under these circumstances there is no clear guidance for the QP of what is within or out with the scope of his/her certification and many of the principles listed in section 11 begin to apply no longer. For example: lines 731-733: In the example supplied above: batches will be released for trial/use without full QP certification Line 773: where final manufacturing steps take place at point of care the QP will not have access to the relevant data where the point of care site is not under the control of the manufacturer. For cell therapy based products delegation of batch release and

		additional on site activities such as reconstitution <i>etc.</i> must be to personnel qualified in the delivery of cell based products.
18	866	Annex 2 of EudraLex 4 provides a definition of a short-shelf-life product (<14 d shelf life). This definition should be adopted for ATMPs with a short shelf life, and not contradicted in additional guidance in an ATMP-specific Annex.
19	N/A	Please provide guidance relating to tests used to determine absence of microbiological contamination, because pharmacopoeial methods rely on absence of turbidity in test media, and most ATMP products are cell suspensions that render test media turbid.
19	922-925	<p>A retention sample for identification purpose is not always possible when the final Drug Product batch size is only one vial for one patient. Would a photograph cover this purpose?</p> <p>For autologous cell based ATMPs even the minimum requirements for reference and retention samples can be a challenge.</p>
19	940-942	Guidance has been adopted by the EC for the retention of samples for imputability testing, following the SoHo V&S project, and its guidance for Communication and Investigations (Deliverable 8). The guidance in lines 940 to 942 is not aligned with this previous guidance, which states that 'archives samples of donor serum or cells... is not a minimum requirement of the EU Directives', though it is encouraged 'as an invaluable tool for the investigation of any subsequent suspected transmission.' Therefore, for autologous ATMPs, such archives are not necessary; for allogeneic ATMPs such archives should be encouraged.
22	N/A	<p>We agree with the principle that reconstitution of a finished ATMP is not the manufacturer's responsibility other than validation of the process and transmission of detailed information about the process.</p> <p>Unlike more traditional medicines, for cell based ATMPs especially reconstitution can have a dramatic impact on the quality of the product. In all cases the manufacturer must ensure that the details for reconstitution have formed part of the overall validation for the product. In those cases where reconstitution can have a critical impact upon the quality attributes of the ATMP the manufacturer should ensure that those reconstitution steps have been fully validated.</p> <p>It should be understood that to ensure this the manufacturer may need to provide additional training, standard operating procedures, detailed equipment requirements that are above and beyond those of more routine medicines.</p> <p>Reconstitution can have a dramatic impact on the quality of the ATMP as received by the patient and it is therefore essential that the manufacturer retains responsibility for these local reconstitution steps. The manufacturer must define both the reconstitution process, and any associated QC and the release criteria. Based on a risk assessment the manufacturer could either:</p> <ol style="list-style-type: none"> 1. For low risk reconstitution (e.g. thawing and diluting), responsibility could be delegated to the hospital.

		<p>2. For higher risk reconstitutions, where the steps could have a significant impact on product quality, the manufacturer should contractually nominate a Suitable Person in the hospital to ensure the reconstitution is carried out according to the manufacturing licence and to assure product quality. The Suitable Person must confirm back to the manufacturer both the validation of the reconstitution process and the equipment, as well as the batch manufacturing record (including QC results) for the specific cell therapy. The Suitable Person would have delegated responsibility from the manufacturer and therefore would need to have defined capability and training. There would need to be a contractual relationship between the manufacturer and the Suitable Person.</p>
23	N/A	<p>Yes we agree that reconstitution should not be part of GMP manufacturing and therefore can be carried out outside of the GMP manufacturing authorisation: for example in a hospital pharmacy or ward but this must be done according to defined and qualified procedures that have been defined and validated/qualified within the GMP manufacturing process and form part of the supply of the medicine. This could involve the manufacturer in the provision of training, SOP's equipment specifications, that would be outside the scope of current standard practices for reconstitution activities.</p>
24	N/A	<p>We consider the following activities to be considered reconstitution:</p> <ul style="list-style-type: none"> • thawing • combining • dilution • removal of DMSO • cutting • grinding • shaping • centrifugation / concentration • filtering (e.g. to remove aggregates during administration) • The removal of contaminants (such as cryopreservative), dead cells, etc. • The addition of a number of different excipients • The addition of a "waking up" period and/or a growth period • Dose sizing (eg number of cells to be given) • The filling of a penultimate (e.g. a bag) or final administration (e.g. a syringe) device
25	N/A	<p>The quality of automated devices that undertake activities that fall into the category of reconstitution in, for example, a hospital setting, should be the responsibility of the site undertaking reconstitution, and not of the ATMP manufacturer.</p> <p>Any activity in an automated device that is true manufacture should be the responsibility of a manufacturer's licence holder (e.g. MIA or MIA(IMP) in the UK). If hospitals are not appropriately licensed then such automated manufacture should not be permitted.</p> <p>The manufacturer should retain responsibility for the manufacturing</p>

		<p>process and for the quality of the resulting cell therapy product irrespective of whether it is made by discrete unit operations or automated devices / systems. The manufacturer of the equipment should remain responsible for delivering qualified equipment. The manufacturer should be responsible for qualifying that the equipment (automated device / system) delivers the cell therapy with the required quality.</p>
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