Client:	N/A	**Validation Doc Number:**			na	
Project:	N/A	**Validation issue:**			na	
Title:	eXmoor response to the Public Consultation Paper on Good Manufacturing Practice for Advanced Therapy Medicinal Products	**Version:**	1	**Page:**	1 of 10	

Abstract:

eXmoor pharma is a biomanufacturing technical and strategic consultancy SME based in the UK and working all over Europe.

Over 50% of its business is in the area of ATMPs and includes process development and design, facility design, GMP compliance and QP certification.

This document is the eXmoor response to the Public Consultation Paper on Good Manufacturing Practice for Advanced Therapy Medicinal Products pursuant to Article 5 of Regulation 1394/2007.

Author	Organisation & Responsibility	Signature	Date
G M Lewis	eXmoor Pharma Concepts	N/A	11 Nov 2015

DOCUMENT HISTORY

Version	**Validation Issue**	**Reason for Issue**	**Date**

1 General Comments:

In general, we feel that it is neither required or useful to have GMP guidelines specific for ATMP's. The consultation document is at risk of implementing a 'GMP-light' system related to the production and quality assurance of ATMP's which we feel would not be beneficial for this emerging market.
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.
Attempting to develop a wide ranging additional GMP guidance for ATMPs without reference to existing GMP guidance is unlikely improve the clarity on EU GMP guidance that is already open to interpretation.
eXmoor pharma Concepts 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 the 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.

It is true that the specifics of development and production of ATMP's bring challenges to the manufacturing and control thereof.
GMP Guidance restricted to those challenges that are specific to ATMPs would however be welcome.
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 base decision making and alongside reference to the existing appropriate guidance

In order to facilitate clinical and commercial production of ATMP's the field would 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.

The consultation document does not make 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.

Detailed definitions of the 'specific characteristics' of ATMPs and the 'specific manufacturing and QC testing challenges (lines 62-63) that are outside the scope of existing medicinal products and GMP guidance would be preferred to a dedicated GMP annex for ATMPs.

Section	Question Number	Line Number	Response
2	1	N/A	The GMP principles laid down in section 2 are in essence already embodied with the existing sufficiently appropriate Eudralex volume 4 GMP guidance chapters and annexes (Chapters, 3, 4, 5 7, Annexes 1, 2, 13, 15, 16 etc.). It would be preferable to only highlight differences from existing guidance
2		97-101	Agreed. There should be no provision for derogations within the GMPs. Specifications within an MA or CTA should be set sufficiently to allow for 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 the variability inherent within certain classes of ATMPs by the acceptance of wider specifications from starting materials all the way through to drug product rather than introduce a principle of 'derogations'.
2.1	2	123-127	It is useful to add the additional level of detail regarding the application of the risk-based approach for ATMPs & highlight some specific areas where ATMPs differ in their risk profile from other medicinal product types. More specific guidance around the risk areas specific for ATMPs would be welcome: For example providing detailed guidance for manufacturers the considerations when undertaking risk analysis and identifying additional control measures.
2	3	N/A	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 and all of this could be covered by cross reference to the appropriate GMP guidance within the directive . 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 the donation, procurement, testing, processing etc. of all cell types used for the manufacture of ATMPs
3	4	N/A	In general the requirements laid out in section 3 are sufficiently well adapted and are covered adequately by existing guidance but the following comments should be taken into consideration: 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?
3	4	147-151	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. For GMO &

Section	Question Number	Line Number	Response
			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 with appropriate levels of secondary containment.
3	4	152-156	These responsibilities and requirements do not differ for ATMPs. Existing guidance fully covers the roles of personnel responsible for product, QC and the QP
4.1-4.5	5	N/A	Generally the provisions laid out in the existing EU GMP chapters and annexes for premises are sufficiently adapted to the requirements of ATMPs with the exception of the use of a grade B background with Grade A working zone for aseptic processing. Here the number of aseptic interventions is many and the period in manufacture is long. 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.
4.2.	5	188	Manufacture in a multi-product facility IS (not maybe) acceptable
		192	Cleaning between batches of the heating, ventilation and air conditions is too stringent. 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. A risk based approach should be encouraged for cleaning and decontamination procedures For closed handlings decontamination of air condition systems would not be relevant.
4.2.2	5	214-215	Premises should be fully 'QUALIFIED' regardless of clinical or commercial manufacture. (To note: This is actually stated in lines 712 and 713)
4.2.2	5	212-215	Regardless of the ability to terminal sterilise or not 'Particular attention should be paid to the filling process'
4.2.2	5	216-219	The risk to maintenance of the aseptic environment is in many cases higher compared to that of standard pharmaceutical products (related to the number of 'open' aseptic processing steps and short shelf life products of manufacturing ATMPs). For that reason, defined guidance of the following should be considered: • 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

Section	Question Number	Line Number	Response
			in EM microbiological testing results within facility/rooms/operation.
4	7	N/A	Where processing is 'semi-open': Consideration could be given the move to a grade C background with and 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. But this should be applicable for both clinical trial and marketed products.
4	8	N/A	This question does not take into account or attempt to make any differentiation between closed and open manufacturing practices /technologies. The manufacture of many routine blood products occurs utilising closed processing technologies in grade D (or even controlled non classified spaces) Current GMP guidance: Annex 1: allows for 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
4	8	N/A	Where GMOs are manufactured in closed systems the use of local grade A isolator with D background is acceptable therefore closed processing of genetically modified ATMPs in a grade D background should not be specifically excluded.
4	8	N/A	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. Where processing is 'semi-open': Consideration could be given the move to a grade C background with and 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.
4	8	N/A	However for truly 'open processes' the following should apply: 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

Section	Question Number	Line Number	Response
			has: • The highest level of open handlings • The lowest defined control strategy and testing of the ATMP product • No or limited validation of QC testing, with the exception • Highest likelihood of patients that have gone through a series of previous treatments and as a result to that are more prone to infections
5	9	N/A	Sufficient guidance is given in existing GMPs, for equipment associated with the manufacture of ATMPs inclusive of early phase clinical studies not required.
6	10	N/A	Sufficient guidance is given in existing GMPs covering documentation practices for ATMPs. There is no requirement for dedicated requirements covering documentation for ATMPs
6	11 & 12	N/A	The existing GMP guidance for documentation practices should be applied to all manufacturing phases from clinical trials to marketed products.
7	13	444-445	There should be a recognition of the inherent variability of the starting materials for ATMPs
7	13	464-469	Agreed
7	13	486	Other methods of sterilisation are acceptable and described within annex 1. Why should heat sterilisation be preferable. Rather any sterilisation methods should be suitable validated and should include all forms i.e. heat, filtration or irradiation.
8	14	538-543	The general guidelines for seed lot and cell banking are covered well within annex 2. However the provisions detailed in lines 538-543 are unique to certain cell based products and as such are required to cover the specific characteristics of ATMPs
9	15	N/A	The general principle for production operations are covered adequately by existing GMP guidance, including for the early stages of development. However there are areas of production where specific guidance would be welcome
9	15	575-579	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 therefore some additional guidance around the minimal expectations when defining critical process parameters and quality attributes would be beneficial. 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

Section	Question Number	Line Number	Response
			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 Specific examples where regulatory guidance would be beneficial are given below: • To what extend 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 material allowed • 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?
9.3	15	630-639	Reference should be made to HVAC design to ensure no cross contamination e.g. use pressure barriers or sinks to contain air within production rooms and not mixing in a common clean corridor
9.3	15	640-645	Manufacturing of gene therapy products should be permissible in the same room as other ATMPs if processes are closed, consideration is given to secondary containment to adequately segregate gene therapy from non-gene therapy products and other risks are managed. I.e. the manufacture of different gene therapies can be manufactured in the same facility provided measures are taken to avoid cross contamination with other products (e.g. see line 639 comment above)
9.3	15	640-645	If segregation is mandated as per the text in lines 640-645 the text fails to adequately describe the requirements. There is no definition of what addition precautions are appropriate, what specific measure should be taken or how 'arrangements for separation should be demonstrated to be effective.
9.3	15	648-649	Additional guidance on the cleaning validation specifically for ATMPs would be beneficial. 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.
10	16	711-713	We are in agreement with this statement but to note it is directly contradicting the statement in

Section	Question Number	Line Number	Response
			section 4 line 214-5
10	16	715-716	The specific guidance given is inadequate given the challenges of devising process simulation tests for patient specific materials and small scale aseptic processes. Specific guidance on the unique requirements of process simulation testing for ATMPs (as exists for small molecules & biologicals for example PIC/s guidance) would be welcome
10	17	N/A	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 limit supply. A formal full validation of a manufacturing process such as practiced for small or biological molecules is often not feasible, it would be beneficial to consider items such as: • Consideration of the use of healthy donor material for process validation (even when it is understood that the results between such starting materials may well differ) • Use of results from early phase clinical productions for completion of the validation package for pivotal and commercial production, even when changes to the manufacturing process are made in between?
11	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 manufacturers' 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
11.1	18	731-733	For ATMPs some Manufacturing activities, such as removal of cryo-protectant followed by re-formulation for patient administration can occur at the point of care. Where this happens these are outside of the control of the certifying QP and within the hospital environment and so the principles stated do not apply
11.2	18	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.
11.3	18	836-838	For Investigation ATMPs QPs are required to certify compliance with the relevant requirements and should create a register that should be available to the competent authority as for marketed products.
12.1	19	N/A	In general the requirements laid down in section 12.1 are as existing requirements.

Section	Question Number	Line Number	Response
12.2	19	922-925	For autologous cell based ATMPs even the minimum requirements as described for reference and retention samples can be a challenge. Specific guidance for the minimum requirements for reference and retention samples specifically for retesting should be provided
14.2	21	1054-1056	Specific guidance of the 'recall' processes required where products have been administered as part of a 2 phase QP certification and release procedure should be provided
16	22	1061	Yes in principle but unlike more traditional medicines for cell based ATMPs especially reconstitution can have a dramatic impact on the quality of the product. This fact places additional responsibilities upon the manufacturer to fully ensure these steps are validated and that centres where reconstitution takes place are suitably qualified to undertake the activity. 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. It should be noted that to ensure centres are suitably qualified to carry out these steps, the manufacturer may need to provide additional training, standard operating procedures, detailed equipment requirements that are above and beyond those of more routine medicines. There would need to be a contractual relationship between the manufacturer and the site. The centre must complete approved documentation (such as a batch record) to confirm the details of the reconstitution step and any associated QC. These must be returned to the manufacturer if required by the agreement.
16	23	1061	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. The centre must complete any associated batch records to confirm the details of the reconstitution step and any associated QC and return these to the manufacturer.
16	24	1061	The items listed in the description for section 16 plus; • The removal of contaminants (such as cryo-preservative), dead cells, etc. • The addition of a number of different excipients

Section	Question Number	Line Number	Response
			• The addition of a "waking up " period and/or a growth period • Concentration • Dose sizing (e.g. number of cell to be given) • The filling of a penultimate (e.g. a bag) or final administration (e.g. a syringe) device
17	25	1062	The manufacturer should retain responsibility for the manufacturing 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. If automation production involves manufacturing activities (as opposed to reconstitution steps listed in section 16 and in answer to Q24 above) the same GMP obligations should apply and those activities should be covered under licence of the site carrying out the automated manufacture The manufacturer of the equipment should remain responsible for delivering qualified equipment. The ATMP manufacturer should be responsible for qualifying that the equipment (automated device / system) delivers the cell therapy with the required quality. To note: the equipment and disposables associated with the reconstitution steps should NOT be classified as medical devices unless they are attached to the patient. They should be classified as GMP equipment and qualified as such.