Response to the Targeted stakeholder consultation on the draft Guidelines on Good Manufacturing Practice for Advanced Therapy Medicinal Products. 28 June 2016 to 26 September 2016

Abstract:

I am responding to the consultation document as a private individual. I am a EU Qualified person with over 26 years' experience working in both the biopharmaceutical industry and 12 years specialising in ATMPs specifically in the clinical setting.

Author	Organisation & Responsibility	Signature	Date
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DOCUMENT HISTORY

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

1 General Comments:

In my opinion the contents of this consultation paper, if implemented, represent a real risk to patient safety, specifically to those patients taking part in clinical trials.

The harmonisation of EU GMP guidance into a single document, followed by all EU member states represents the highest level of protection for patients.

This consultation paper appears to be diverging from that concept, to the detriment of the patient.
The attached represents a few of my specific concerns.

Overall: The majority of the principles contained in the paper are already embodied in EudraLex Volume 4. These MUST be maintained as the EU GMP standard that ALL manufacturers of medicinal products (ATMPs and others) adhere to. The addition of an annex detailing the few specific requirements pertaining to ATMPs would be welcome.

I do not believe that an adaptation of the GMP guidelines specifically for ATMP's is beneficial or instrumental to protecting the patient .

As this draft guidance document is written it is unclear where it is planned to sit within current EU legislation covering GMP production of medicinal products. The inclusion of some but not all aspects of GMP currently described within EudraLex volume 4 suggests that it is to be viewed as a standalone document; in which case it fails to provide sufficient depth, has serious omissions, and will create more uncertainty rather than providing clarity and simplicity.
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 must be avoided.
It should to refer to existing GMP standards within EudraLex volume 4 and give advice (via an additional annex potentially) on the application of a risk based approach to the manufacture of ATMPs where a flexible approach is required.

Attempting to develop an additional GMP guidance for ATMPs without reference to existing GMP guidance will not improve the clarity on EU GMP guidance that is already open to interpretation.

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.
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.

ATMPs are high risk medicines manufactured for high risk patients and, as such, they warrant the highest standard of GMP throughout the lifecycle of the product.

Rationale for our assessment that ATMPs are high risk includes the following points;

- They are aseptic products, with no terminal sterilisation steps, susceptible to contamination in that they often have a protracted incubation period and are growing in nutrient rich media.
- Manufacture can involve open systems
- Differentiation may occur during manufacture compared to their source cell type.
- They are often QP released for use prior to all QC test results being available.

- They are given to susceptible patients often using novel administration techniques,
- Due to their mode of action they are retained and may proliferate in the patient

Pre-clinically these products are often innovated by academic researchers whose focus is not routinely on patient safety. The transfer to a GMP environment is therefore critical to ensure the potential benefits of these products are translated safely into medicine presentations with a quality assured specification. A 'dilution' in the GMP standards required could lead to patient harm which will inevitably delay progress in the field and stifle the progress with these innovative products.

ATMPs are emerging as a global industry. The draft document gives no information with regard to the degree of harmonisation to existing international standards (e.g. PIC/s, WHO, ICH) which is a point of serious concern since ATMP development is truly international and medicines are often in trials in multiple jurisdictions.
It is essential that ATMPs and advanced therapy investigational medicinal products (ATIMPs) made within the EU are considered fit for import into countries outside of the EU; particularly as these medicines approach commercialisation. As this draft guidance stands there is a danger that it will not be recognised by third party countries such as the USA, Japan etc.

A similar concern exists around the processing of tissue and cell products which are not classed as ATMPs. Currently the EU tissue and cells directive relates directly to annex 2 of EU GMP which then references the standards for annex 1. The adoption of this draft guidance would create a double standard with the healthcare setting with the processing of lower risk non-substantially manipulated cells and tissues being regulated to a higher standard than ATMP medicines. This is not logical and must be avoided.

A further risk of these guidelines is a perceived reduction in quality of ATIMPs, and, either a subsequent increased risk of failure to develop to the standard required for a marketing authorisation, or (eventually) a reduction in the rigour applied to obtain a marketing authorisation for this group of high risk medicines which would be detrimental to both patient safety and potentially could erode the public confidence in the regulation applied to medicines generally.
This is a real problem and is demonstrated by the difficulties being faced by commercial drug developers trying to move from early phase academic trials in the US to late stage commercial trials and marketing authorisation. The lack of rigour in cGMP manufacture in academic sites in the US has led to significant gaps in process development so promising results in academic phase II trials have delayed transition to phase III and registration because the whole manufacturing process has to be re-engineered to meet a standard fit for a licensed product. This delay in product development can kill a promising medicine because the field moves so fast that the phase III trial can't even enroll patients since the next generation of the product is already available for early phase trials and these are seen by academic clinicians with the appropriate patients as more exciting and have a greater chance of high impact publication.
For ATMPs it is important to ensure that the expectation is that ALL medicinal products comply with EU GMP expectations throughout the product lifecycle from validation through phases I, II and III clinical trials and ease the pathway to marketing whilst ensuring patient safety via optimal product quality. It is particularly disappointing that the validation requirements of annex 15 have been largely ignored in this draft.

There is a new Clinical Trials Regulation being introduced into Europe, and that this new regulation allows for some flexibility in relation to phase 1 studies. ATMPs used as IMPs should not be considered exceptional and should fall in line with the new clinical trials regulation. It may be useful for the GMP guidance to give an indication/examples of the required release specifications for ATIMPs during their development i.e. minimum specification requirements for Phases I, II and III. This would then overtly encourage developers to begin to define potency and impurity assays etc. at an earlier stage.

Some generic and specific comments are given in response but overall I reiterate that this document represents and unprecedented and unwarranted diluting down of EU GMP harmonised standards that, if implemented would represent a substantial backwards step in the development of the emerging ATMP sector. In addition many aspects of the guidance document would see an increased risk to patient safety especially those relating to investigational ATMPs

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Section	Line Number	Response
ALL	N/A	The GMP principles laid down in Eudralex 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
1	107-127	The pharmaceutical quality system is not further described than in the introduction. It is a very limited description and should refer to more detailed guidance, for example, ICH Q10 in which more detail and reference is also made to: -Management of outsourced activities -Continual improvement of process performance and product quality, including pharmaceutical development (ICH Q8) -Preventative actions (not just quality defects/corrective actions) -Change management: VERY important in development of ATMP manufacturing process to track and qualify changes TO NOTE: ALL THESE ASPECTS ARE COVERED CLEARLY IN EudraLex Part 1 chapter 1
2.1	ALL	This section provides some detail to specific ATMP related hurdles. But there is no reference to what compliance to risk management approach is expected, e.g. the general expectation how to approach a risk analysis (ICH Q9) describing risk identification, - analysis, - evaluation incl. probability and uncertainty
2.3.4	ALL	ANNEX 13 of EU volume 4 covers the aspects of flexibility for IMPS. The aseptic nature of ATMPs increases the safety risk to the patient. This section makes no mention of defining & validating patient critical safety steps & reduces the requirement to set specifications. Adoption of these guidelines would significantly reduce patient safety
2.3.4 4.2.2	322-327 516-519	This is not a suitable environment for the open processing of aseptically prepared products with no terminal sterilisation steps. This processing makes them susceptible to contamination in that they often have a protracted incubation period and are growing in nutrient rich media. Additionally these products are often QP released for use prior to all QC test results being available. A grade C background with A environment does not provide enough safety protection for the patient. This directly contradicts the requirement defined in lines 516-519. It cannot be acceptable to put clinical trial patients at undue risk of contamination due to inadequate manufacturing environments THIS MUST NOT BE PERMITTED FOR ANY PHASE OF TRIAL & SETS A PRESIDENT FOR THE MANUFACTURE OF MARKETED PRODUCTS

Section	Line Number	Response
2.1	ALL	This section provides some detail to specific ATMP related hurdles. But there is no reference to what compliance to risk management approach is expected, e.g. the general expectation how to approach a risk analysis (ICH Q9) describing risk identification, - analysis, - evaluation incl. probability and uncertainty
3.1	346-348	If this is a stand-alone document, this section is very weak compared to EUDRALEX volume 4 chapter 2 in: -Key personnel to include head of production, head of QC & QP – TO NOTE: ALL THESE ASPECTS ARE COVERED CLEARLY IN EudraLex Part 1 chapter 2
3.2	352-357	As a lot of processes will remain manual, open for coming years, I believe more guidance in minimal training requirements Completion of A single process simulation test is not adequate to demonstrate training in these complex and often long aseptic processes
3.2	365-366	Reference is required to training of staff collecting starting material (e.g. blood collection) and handling of drug products prior to administration to patients. The variability in collection and handling of DP at hospitals is a challenging part in the supply chain
3.3	376-401	TO NOTE: ALL THESE ASPECTS ARE COVERED CLEARLY IN EudraLex Part 1 Annex 1
3.3	383	Implies no gloves required in Grade C & see risks associated with open manufacturing of IMP ATMPS in lines 322-327
3.4	ALL	This section makes only passing reference to the QP & takes lines directly from Eudralex volume 4 chapter 2 & is in the wrong place in relation to this document.
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Section	Line Number	Response
4.2.3	549-550	There are many differences in approach taken by ATMP manufacturers in the level of monitoring during operation and in rest, location. Specifically evaluating the risks, EM validation program and active sampling during operation. We strongly believe it should be mandatory to perform monthly trending of EM results, with preventative measures at certain alert level. This is important for ATMP manufacturing as many handlings are performed in open manner and products need to be released undue time pressure without final sterility testing results available
5	660-661	What about making aseptic connections using validated welding & sealing systems that are currently carried out in grade D and C backgrounds and how does this compare to the use of isolators in a grade D or C environment. This statement contradicts the production using closed processing to make these connections
6	693-708 786-799 855	What about other documentation critical for the quality system, e.g. policies, validation and testing protocols, This fall well short of the documentation requirements detailed in Eudralex Volume 4 chapter 4 The details listed for the contents of the PSF fall short of the requirements referenced in Eudralex volume 4, Annex 13. The PSF is the manufacturing and testing specification for the product. The requirements listed here would not allow the manufacturer to develop master batch & testing records from this. There is no mention of stability data and the PSF is not the place to record the documentation for blinding and un-blinding procedures. The statements in this section demonstrate a complete lack of understanding of the requirements for blinding and un-blinding with respect to clinical studies. There is no mention anywhere of the labelling requirements specific to clinical trial materials What about complaints procedure and change controls, training etc. etc.
7	931-933 948-951	How do you propose 'growth promoting properties of culture media be demonstrated to be suitable for its intended use' These media are often designed by the supplier for the sue intended. Is that enough or do you expect manufactures to demonstrate this? There is no mention of the Product Specification File as required for IMPs and part of the requirements for QP certification in accordance with the relevant directives
8	1085-1090, 1122-1129 & 1131	Under what criteria are the competent authorities going to approve the use of starting materials from cell stocks/cell banks and viral seed stocks generated (in the past) without full GMP in the manufacture of an ATMP?

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Section	Line Number	Response
9.4	1226 1234-1236	ATMP products do not routine undergone sterilisation at any stage in there manufacture, being aseptic products so are at risk all through the manufacturing process not just at filling What is the content of self-contained production area – would separate HVAC be require or separate production suite? What is meant by campaign basis: production in segregated area, performing cleaning and use production area again directly after (based on validation of this procedure) Or Production of the full batch time (weeks?) before allowance to use production suite for other process/product/batch?
9.5	1267-1274	The definition of closed systems used throughout the document seems unclear. Here it seems like a closed system is described as an isolator in which open handlings are performed. Closed system could also be seen as closed culture system / bag / tubing with sterile welding. In another part of the document, closed system is described as allowed to be performed in grade D area. These texts seem contradictory Would it not be allowed to perform class A open handlings in a clean room (class B) which hosts an incubator which is used for a differed batch/product?

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9.5	1294-1295	The mention of double ended autoclaves specifically relates to final fill & finish requirements related to more traditional medicinal products & seems out of place here
	1296-1300	The use of multiple wrapping & unwrapping for transfers to the clean area will require validation and what are 'appropriate sanitisation precautions' For ATMP culture media what does 'sanitised in situ' mean. This usually refers to fermentation processes. ATMPs are not usually manufactured in a fermenter where media can be sanitized as described.
	1364-1347	What time & what temperature: there is no guidance given
	1326	Define the term 'verified' Where filters are supplied 'pre sterilised' would a C of A for verification be suitable?
	1330	Why would you permit the use of the same filter for a day? This seems nonsensical and would open up the product to unknown contamination risk
10	N/A	The general approach to qualification and validation is laid out in Eudralex Volume 4 Annex 15.
	N/A	There is no mention of the requirement for a Validation master Plan
	1469-1471	Here there is no mention of Design Qualification, System Impact Assessment
	1459	This makes mention to grade 'A' ROOMS. What is a grade A room?
	1490-1493	How is it intended to demonstrate that the functionality of a piece of equipment is not affected by transport & the requirements for qualification begin at IQ in this document (line1469-1471) i.e. there is no mention of FAT testing?

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11	All	There are 21 routine duties of the QP identified in 1.7 of Annex 16 of EudraLex Volume 4. This guidance has merely 13. Steps omitted from the draft guidance include the following: • The entire supply chain is documented and available to the QP. • All audits of sites involved in the manufacture and testing of the product have been carried out and that the audit reports are available to the QP prior to certification. • Sites of manufacture and testing are compliant with the terms of the MA (or CTA) for the intended territory. • All manufacture and testing activities are compliant with the terms of the MA (or CTA). • Active substances have been manufactured and distributed in compliance with GMP and GDP for active substances (EudraLex Volume 4 Part II). • Manufacturing and testing remain in a validated state and that personnel are trained and qualified. • Any ongoing complaints investigations or recalls do not negate the conditions for certification of the batch in question. • Technical agreements are in place. This is an example of divergence in GMP guidance, which could lead to an independent requirement for special QPs that follow separate guidance and are not able to certify products other than ATMPs. The harmonised and legal duties of the QP are designed to ensure the safety, quality and efficiency of each medicinal product. These duties are detailed in EU law. The duties are detailed in chapters 2, Annex 16 and Annex 13 for IMPs. The must be no divergence from these legal duties for ATMPs
11.2	1658-1663	Where is the EU, where it is common practice for only registered pharmacists to be QPs will you find pharmacists with training & experience in cell and tissue biology, biotechnological techniques, cell processing, characterization and potency testing?
11.2	1664-1669	There is no mention of the Product Specification File for investigation ATMPS. Ref EU Annex 13 and relevant directives. The IMP ATMP must be certified in accordance with GMP, CTA and the Product Specification File

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11.5	1809-1817	This implies that any out of specification result would be acceptable. Does this include safety critical OOSs?. The existing legislation (i.e. legal requirements) covering QPs does not allow for the certification of products that do not meet the specification. How do you propose to handle this divergence. Are you planning to make amendment to the EU directives covering medicinal products> How do you intend reprocessing takes place: this is generally not allowed for other products and would seriously impact on the viability (for example) of a cell based product. This decision appears to be in the hands of the manufacturer & the physician and not the QP & physician
12	ALL	
13	1991-1996	There is no mention of the GMP requirement for a Technical Agreement that details all the GMP responsibilities for each party
14		
15	ALL	The management, classification and control requirements for handling of GMOs are detailed in other guidance documents & the responsibility of different authorities.
16	2089 2094-2095 2100-2101	There is no mention of the washing & centrifugation for the removal of cryoprotectant. Is the classed as reconstitution or manufacture? This must be conducted in an appropriate environment to maintain the aseptic nature of the product & that environment must be validated for the purpose This implies that the administration site is GMP compliant. What makes an administration site 'GMP compliant' & what 'GMP' are they expected to be compliant with?
17	ALL	Generally this section is confused and confusing. There are contradictions with statements in section 16 for example: lines 2100-2101 state that the administration site needs to be GMP compliant but this section makes reference to operating theatres

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17.4	2171-2181	How would you prove that the conditions in the operating theatre where adequate? Why if the validation data supports its use is a ward not acceptable as an environment
17.6	2199	Batch CERTIFICATION is a fundamental requirement & certification and release may occur at different times but a product cannot be released unless it has been certified

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