ReNeuron Limited

Comments on the Consultation Document

Good Manufacturing Practice for Advanced Therapy Medicinal Products

General comments

1. As an SME working in the research, clinical development, manufacture and future commercialisation of Advanced Therapy Medicinal Products (ATMP), ReNeuron Limited welcomes the clarification of GMP requirements as they relate to the specific challenges associated with the manufacture and testing of ATMPs.
2. Notwithstanding our general support for the concept of the guideline, we have significant reservations about the text as it stands and how this guideline should be read in relation to the wealth of existing GMP regulations (Directive 2003/94/EC) and guidance (Volume 4 of "The rules governing medicinal products in the European Union"). The current draft document does not make clear whether these ATMP guidelines are proposed to be stand-alone guidance for GMP for ATMPs or whether they are a supplement to the existing Volume 4 guidance documents and Annexes. The extensive text suggests the former but it is our view that this is not the appropriate approach and that these guidelines should be a new Annex to Volume 4, in the same way as for example Annex 3 on radiopharmaceuticals, another very specialised type of medicinal product. We would suggest that the new Annex cross-refers to existing text in Parts I, II and the Annexes to Volume 4 in the same way as the other Annexes do currently. We believe that the majority of the text in the existing Volume 4 is relevant to ATMPs and the new guideline should simply address those specific areas where a different approach may be warranted for ATMPs.
3. Furthermore, Annex 2 on Manufacture of Biological Active Substances and Medicinal Products for Human Use already has text on gene therapies and cell therapy products. We assume that this text would be removed from the current Annex 2. We agree that this text is not sufficiently detailed and could be significantly improved, but we also agree with the concept already adopted for ATMPs - that GMP requirements should be specified in a specific annex that cross-refers to other sections of Volume 4 as appropriate. We believe that creating a specific, stand-alone text for ATMPs risks duplication and potential confusion in the interpretation of requirements and that adopting the current philosophy of general GMP requirements supported by a specific Annex would avoid these risks.
4. ICH Q9 principles of Quality Risk Management should be more clearly referred to in this ATMP guideline and a risk based approach encouraged.
5. The ATMP guidelines should not weaken GMP requirements to cater for small scale production of ATMPs in hospital or academic environment, especially in the area of microbiological control of the environment of production. There are a number of inherent risks associated with ATMPs that are not related to the GMP manufacturing environment and which are difficult to minimise (e.g. potential for tumourigenicity, complex methods of administration, product stability). We believe that where risks can more easily be minimised, for example by control of the manufacturing environment to reduce the risk of microbial contamination, that GMP requirements should not be downgraded for ATMPs compared to

other biological products and in this way the overall risk of the product is reduced. Other biological products are less complex, can often be terminally sterilised and can include viral inactivation/removal steps and it therefore seems illogical to make the requirements for the clean environment less onerous for ATMPs, where these measures often cannot be employed.

6. A single standard of GMP should apply to all manufacturers (commercial, hospital, academic) as different approaches will have the effect of reducing GMP standards across the board. The overriding principle should be to define systems of GMP that assure as far as possible the safety of the patient. This should apply regardless of the manufacturing source of the product. It is noted for example that GMP for radiopharmaceuticals applies to Nuclear Centres/Institutes and PET Centres as well as industrial manufacturers.

Specific comments on the text

Please see the table below for specific comments on the text of the draft guideline.

Section Heading	Line number	ReNeuron comment
2. GMPs for ATMPs: general principles	85-87	The terms “starting and raw materials”, “intermediates and bulk products” should be defined more clearly as the concepts are different for ATMPs compared to other types of biologicals. Cells can be the starting material, drug substance and drug product for ATMPs.
2. GMPs for ATMPs: general principles	97-101 This comment also applies to lines : 462-463 797-798 829 956	This should be modified to say “….foreseen in the marketing authorisation **including subsequent variations and annual report changes** or clinical trial **authorisation including subsequent substantial and non-substantial amendments/modifications** should always be adhered to.” It is critical especially in the clinical development phase to remember that the approved clinical trial authorisation consists of the initial submission, approved substantial amendments **and non-substantial amendments**. It is important to avoid the interpretation from this GMP guideline that all (including non-substantial) changes must be notified to the competent authority that has approved the CTA in order to always have an up to date IMPD approved. This requirement would go against the requirements of Directive 2001/83/EC and the new Regulation 536/2014 which state that only substantial amendments or modifications need to be approved by the competent authority and would significantly delay clinical research with ATMPs. While we understand that this should be generally understood and should not need to be re-iterated here, in practice there is a tendency for over-reporting of non-substantial amendments. With the complexity of ATMP manufacturing processes, minor changes to the process are more likely than with other types of products and it would therefore be useful here to specifically re-iterate the concept that the CTA approval consists not only of what has been filed with and approved by the regulatory agencies but also of minor changes listed as non-substantial amendments and kept internally within the sponsor company prior to notification at the next IMPD update. In addition to this point, we would like to see increased flexibility on the part of the QP to allow release of product (in the clinical trial phase) that may not have followed exactly the letter of the approved IMPD, based on a risk-assessment of the deviation. Relating to our general points on the guideline above, we feel that flexibility is being suggested in the wrong places – for example on facility qualification, environmental background, when in

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		fact limited flexibility on the process side would be more beneficial in promoting faster completion of clinical trials and therefore access to new products by patients. We also believe that limited flexibility for minor process changes would be of significantly lower risk to the patient than some of the suggested flexibilities on environmental controls proposed in the guideline.
4 Premises	162-166	There is guidance on designing facilities to mitigate the risk of cross-contamination but no mention of control during building of premises. If this text is to replace Annex 15 it needs to be expanded, however in accordance with our general comments on the guideline, we would recommend cross-referring to Annex 15 and using the text here only to describe ATMP specific aspects.
4.1 General principles	167-181	Should just follow Annex 1 – see general comments.
4.2 Production areas	195-201	This text implies that an inspector could cite a breach when an actual deviation has not occurred. As long as appropriate controls are in place it should not be necessary to specify this. It is unclear what is specifically different about ATMPs in this respect.
4.2.2 Aseptic environment	214-215	We don't agree that validated premises should only be required for commercial product. IMPs should not carry additional microbiological risk or other risk introduced by not validating the plant properly. While this risk could be mitigated with extensive microbiological monitoring, we believe this would be more onerous than validating the facility. Currently in Europe, all IMPS are manufactured under the same GMP requirements for aseptic environment validation and this is achievable in our view. Later on in the document (lines 714-715) it states that the aseptic processes must be validated. It is very difficult to achieve that if the facility isn't validated. This seems contradictory and we believe that the facility should be validated during the clinical trial phase of development.
4.2.2 Aseptic environment	230-233 and Q8	We do not understand why an "A grade with a background of C or D grade" would be allowed for early phase clinical trials as opposed to later stage and commercial. These products are all intended for patients and this increases the risk of microbial contamination. It is possible that more extensive monitoring could be employed but it would be difficult for regulatory authorities to enforce this through inspection considering the number of sites involved. It will allow a divergence away from current acceptable standards and practice and problems will only be picked up when a patient

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		experiences a major infection. As a general rule, we believe that the risk to the patient in clinical trials should be from the novelty of the product itself (which is unavoidable) and not from reducing the microbiological control of the manufacturing process (which is avoidable). We could see the use of more contained Grade A environments such as RABS/Isolators within lower background environments as long as there is proof that the lower background environment does not impact the grade A environment. This would be for all phases of clinical trials.
6. Documentation	427-428 and 438-441	Paragraph starting on line 438 states traceability requirements mean data need to be kept for 30 years as required by the regulations. This however appears to be contradicted by the paragraph starting line 427 where batch documents are to be kept 1 year post expiry of the batch or at least 5 years after certification of the batch by the QP. The batch record also needs to be kept for 30 years, especially when CMOs are used, to ensure traceability.
6.1 General principles & 13.3	306 & 1012	These lines put contracts in the scope of regulatory inspection for GMP which hasn't traditionally been the case. We would prefer to see the mention of quality and technical agreements rather than contracts, because it is the quality aspects that are open to inspection rather than the commercial terms of contracts. This would be more in line with existing GMP requirements.
8 Seed lot and cell bank system	522-524	We are unsure why population doublings has been specifically mentioned as a critical process parameter. Depending on the particular cell line, a number of other parameters could be equally important to control.
8. Seed lot and cell bank system	538-543	We are unclear on this paragraph. Is it referring to autologous products? It should be clarified with definitions (e.g. of cell stock).
8. Seed lot and cell bank system	553	We are unclear why containers could not be returned to stock provided that they have been held in the GMP supply chain and stored correctly.
10 Qualification and validation	711-713	Aseptic process validations are conducted in order to demonstrate that a particular operator, using particular equipment, under particular environmental conditions can produce material that is sterile. It is a snap shot in time. The rationale behind that snap-shot being representative is that the equipment and environment are validated, thereby assuring that the same conditions are replicated time after time during product

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		manufacture. Therefore it appears contradictory to state that APVs must be performed but that environment and equipment need not be validated as per lines 214 and 215.
10. Qualification and validation		For ATMPs it makes sense that a model of continuous process verification should be adopted, which allows for parameters and associated acceptance criteria to be continually evaluated against identified CQAs, i.e. if a parameter is outside of a limited proven range, but within control (as per statistical tools i.e. Shewhart control charts) the parameters may be altered. The aim of validation here is clearly very much about maintaining and demonstrating control of the process, understanding that there is increased variability inherent in biological and especially ATMP processes.
11.2 Qualified person and batch release	745	Please refer also to comment on section 2 above. It needs to be very clear that the clinical trial authorisation consists of the initially approved CTA, submitted substantial amendments and **the list of non-substantial amendments** required to be kept by the sponsor (see paragraph 132, section 3.6 of 2010/C 82/01 (CT-1 guideline). Release by the QP should be against all three of these, including the list of non-substantial amendments. This should be specified here because this is not always clear to QPs that the list of non-substantial amendments can be considered as part of the approved CTA and this leads to the potential to require submission of amendments to the regulatory authorities that should not be submitted, or non-release of the product. Both significantly delay clinical trials unnecessarily. Furthermore, we believe that considering the special characteristics of ATMPs, including the complexities and cost of production, the QP should be allowed some discretion in releasing batches for which a deviation from the approved details in the IMPD may have occurred. This discretion would of course relate to minor deviations for which a risk assessment had been conducted and for which a conclusion of minimal risk to the patient had been reached by the QP. This would reduce the potential need for "batch specific" amendments to be submitted to regulatory authorities and therefore reduce delays in clinical trials.
11.2 Qualified person and batch release	757	This should not be restricted to autologous products as it could apply also to allogeneic products. Furthermore, the issue here is not just for products available in very small quantities. The analytical techniques used for ATMPs are often complex and can be very difficult to transfer. In justified cases, this should also be a rationale for not performing complete re-testing in the EU.

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11.3 Batch release	839	Why only 5 years' storage when ATMP regulations require traceability for 30 years? See also comment on lines 427-428 and 438-441.
12.3 Testing	957-958	This section cross-references Section 10 but analytical validation is not mentioned in section 10. There is no guidance here on the phase of development – other sections discuss the difference between the understanding of the process etc. at different phases – but there is nothing here in terms of the analytics at different phases.
12.3 Testing	982-986	We disagree that this shouldn't be an expectation for IMPs. The data should be trended as part of the control strategy to determine critical quality parameters. This is part of the process development that goes on through clinical development.
16. Reconstitution of product after batch release and	1061	Q22. Agree with principal but must also include training (and sign-off) of hospital staff. Q23: This depends on activity. For those activities mentioned in response to Q24, we agree. Q24. Any activity that does not run a significant risk of fundamentally altering the characteristics of the product including compliance with specifications set by the manufacturer, stability or other quality characteristics. Typically this would include dilution, thawing and dispersion.
17. Automated production of ATMPs	1062	Manipulation of the cells at the hospital is the hospital's responsibility. This is why definition of where the DP is actually produced is so important. Drug product should be released by a QP, and if product is actually made into drug product at the hospital (re-formulated for example) there should be a QP release but by a QP on the hospital manufacturing authorisation – using a QP-QP agreement with the releasing QP from the manufacturing site. The manufacturer of the automated system should also bear responsibility for ensuring that the process can be conducted according to the principles of GMP at the hospital.