Dear Sir/Madam

I have been involved in Industrial cell therapy manufacturing and development since 1987 both in the US and EU and I would like to make some personal responses to the consultation document which on the whole is very helpful but I think if its intention is to act as a stand alone document then it could be made clearer and have additional information within it. Specifically

1) I think the environment grading could be explained better. Grade A-D is mentioned in several places and in two tables but a summary upfront would help. Also to define what is meant by "background" would clarify things. see lines 299-302

2) The document doesn't explain the situation for exempt products i.e. hospital exemption, are these to be treated as marketed or investigational ATMPs? see lines 309-313

3) I think it is extremely important that what is (and what is not ) meant by substantial manipulation should be clarified. This is currently a grey area.

4) In lines 516-519 it states "Grade A with background of grade B is required" but in lines 299-302 it says "Under no circumstances it is acceptable to conduct manufacturing operations in premises with air quality classification lower than a critical clean room of grade A in a background clean area of grade D" and then in lines 322-324 it says "For first-in-man clinical trials, production in an open environment may be performed in a critical clean area of grade A in a background clean area of grade C if appropriate controls of microbiological contamination, separation of processing procedures, and validated cleaning and disinfection are put in place". These somewhat contradictory statements could be clarified

5) The tables at lines 530 and 560 could be combined and shown earlier, together with clothing from 378 (see my comment 1)

6) There are several mentions in the document of "closed systems" but no real definition of what this means. Can systems be open and closed at different times? Is a flask that is sealed a closed system in an incubator and an open system when media is being transferred? Is a system closed if all the vents etc protected by 0.22 micron filters? etc

There are very different requirements in this document for open vs closed systems and I think without proper definition this could create considerable incentive to describe systems as "closed" for example in line 594 it states in a closed production system the risk of contamination from operators can be reduced and 595 therefore the frequency of monitoring can also be reduced but in lines but in line 506 it says "Production in a closed system5 or in an isolator: a background clean area of D grade is 506 acceptable" which would suggest contamination in a closed system is negligible

7) Line 1069 I think again additional clarity could be provided concerning definitions of seed lots and cell banks. What is intended her by a "seed lot".

Also passages and population doublings should also be better defined as they are often been as interchangeable and the risks of these should be better defined. for e.g. reducing the number of population doublings per passage reduces the chance of overgrowth of a subpopulation with shorter population doubling time but increases the risk of contamination because of the increased number of manufacturing steps.

Also it would be helpful to provide some guidance as when and how production could change from different banks and/or donors specifically regards to clinical equality etc

8) Better definition of the quality of clean steam would be helpful in terms of contamination risks. Does clean steam mean WFI steam etc.

9) The descriptions in lines 1267-1313 is very welcome though again the definition of "closed" would be helpful. For example would different T-flasks fitted with filter caps be considered closed when in in an incubator if suitably validated?

10) line 1647 I think it is extremely important to explain in this document, if it is intended to stand alone, what is meant by "certification by a QP". Does this for example mean that every BMR needs to be reviewed fully and signed off by a QP? or does he need to certify that the BMR was completed and reviewed? There is a critical shortage of ATMP trained QPs plus even if available the scarcity of such QPs means that the costs of individual BMR review by a QP (especially of autologous products) is considerable and often exceeds all other costs in manufacture of a batch of product. The risk based approach of when and how to use a QP and the possible roles of a "designated person"would be VERY helpful here specifically regarding what is meant in lines 1764-1768 and 1782-1785

11) Line 1868 It is unclear often what is meant be "not always possible" with regards to sample retention. It may be physically possible but not commercially possible to retain sufficient samples and it would be useful to describe what could be done to decide this.

12) line 1876. Some clarification here on options of a suitable sampling plan would be helpful and whether this could be modified with confidence as to batch homogeneity etc

13) Line 2130. I am not sure that this is very clear. Does this mean that a piece of automated equipment could be used to produce an ATMP if it was not itself validated by the manufacturer for GMP production? There is a specific case here in that TAP biosystems has produced a compact select that many people have used for cell culture. However it is very unclear whether this piece of equipment could be used to manufacture an ATMP. If validated by the specific ATMP producer that this equipment was suitable for a specific ATMP, could this then be used?

Please don't hesitate to contact me if you need additional clarification. I think this is an extremely important document and could greatly benefit this sector and you are to be congratulated on bringing such an innovation risk based approach to this.

regards