Consultation of GMP for ATMPs:

Comments done by:
L Barnouin
QP, TBF Génie Tissulaire,
6 rue d'Italie 69780 MIONS, France.

Q1: Principles in section 2 are sufficient. Introduction could point out that instead development done in hospital, ATPMs quality control techniques are moving rapidly, biological characteristic could be changed between research, development and scale increasing of manufacturing and need to be adapted for pharmaceutical sector, so early as possible quality and manufacturing practices need to be followed as soon as possible.

Q2: ATMP need to have risk management process during very early stage because specifications or variability of biological product need to be carefully managed and as soon that the product is manufactured in hospital or in academic, following Annex 15.
A risk-based approach is very important: for example, a rediffferenciation of stem cell could appear in a range of days but sometime very late. The rejection of the cells need to be based on risk-analysis with all other quality control and then followed with data of clinical trial for example.
Extreme situation need to be analyzed, in the risk analysis as soon as possible following sometime the preciosity of the starting material.

Q3: The release of the staring material as tissue and cells need to be done by a tissue Bank with competent authority authorization to qualify quality and safety. The tissue Bank will follow the step between procurement and delivery.
Jacie is only adapted for hematopoietic cells, most of tissue bank have a quality system; Inspection by tissue and cell competent authority need to cover this field. Guidelines of Tissue and cells practices are available in some countries.

Q4: The requirement of personnel could be reinforced in the text, with continuously qualification and regarding specific training with method or process not described in some guidelines or pharmacopeia.

Q5: Requirement could add that premises need to be appropriate related:
- No cross contamination
- With medicinal product but also starting material and raw material which has also biological activity.

Q6-Q7: premises need to be adapted with manufacturing of small batch or individual batch at the same quality of large batches. Flexibilities could be organized by control or storage (raw material, finished product..) premises in first in man clinical trial or pivotal clinical trial; but not for manufacturing .

Q8: The clean room has not to be down graded for early stage, no risk of microbiological contamination need to be added, and antibiotics need to be limited. A in C in D is not acceptable. Some contamination of mycoplasma could occurred for long time in cell therapy and it is know that 5% of cell lines are contaminated by bacteria in the world.
Cleaning validation with risk analysis is very important.

For this part, the writing is important related to the definition of

- Starting material
- Raw material which could have biological effect
- Active substance
- Or medicinal product.

All of them need to be covered by a strategy to limit cross contamination.

Q9: Text regarding equipment is appropriate.

Q10-11-12: the text is appropriate. Documentation is the key for transfer to the first in man manufacturing, to clinical trial to commercial step.
The batch documentation only one year after expiry seems short (biological expiry product cold be only few hours or days)

Q13:
Additional information in batch processing record regarding biological raw material.

Additional writing related starting material **and** biological raw material.

Q15:
The text is appropriate, manufacturing included mostly biological raw material, which need to be included in the manufacturing guidelines.

Q16-17:
The text is too restrictive for investigational product, some validation need to be done as cleaning validation or some process validation. Because some ATMP with biological activity can be linked to clinical efficacy; critical step including transportation need to be validated (maybe not extensively). This validation could be done with risk-analysis of these critical processes, and adapted for investigational ATMP.

Q18-19: no comment
Q20-21: no comment

Q22: reconstitution of finished product is required, and need to be validated as transportation until the use. The reconstitution is not GMP environment but is the responsibility to the sponsor or the marketing holder. It is not clear that reconstitution is not the responsibility of the manufacturer because specifications could be modified during this step. (example during transportation finished product in transport media could have biological change)
Risk analysis of reconstitution need to be considered as a specific validation.

Q23: Automated production need to have as minimum ISO13485, or tissue and cells good manufacturing practices guidelines.
The GMP manufacturing could be minimized but personnel, validation, quality control, documentations, and release need to be covered.

Mions 12/11/2015

L Barnouin