To whom it may concern

Greven, Sept 09 2016

Dear Sir/Madame,

Please find below our comments re the above consultation document:

General comments:

We believe that the document makes several important statements/clarifications specific to ATMPs, in particular, when it refers to ingredients specific to ATMPs or the sometimes short shelf live.

On the other hand, we perceive this document to make frequently abbreviated statements in regard to topics covered in depth elsewhere.

Based on these considerations we recommend to implement changes to existing documents such as EU GMP rather than to produce a new document, which may be an abbreviated duplication.

The sections on premises and personnel may suffice as examples – these appear to be abbreviated descriptions of what is found elsewhere.

Statements such as “High level” or “the level of documentation will vary”. From the manufacturer’s point of view it would be preferable to have clear cut statements. Delays in the approval process arise in particular from negotiations with regulators and/or consultations within agencies. Consequently, anything which minimizes the need for such actions is likely to minimize the duration of an approval process.

Our detailed comments (line number, comment):

145 Risk based approach

We welcome the explicit mentioning of taking risk based approaches. However, we believe that this is inherent in GMP in general and hence does not warrant specific guidance for ATMPs.

160 We appreciate the flexibility mentioned as indeed often the mechanism of action is understood only partly

165 We note that the document states that hospitals often use quality systems different from typical ones – while that may be true, we do not see a reason to grant such exception to hospitals as we would expect them to operate under the same guidance and scrutiny as other manufacturers

191 ff agreed, additional flexibility in early clinical studies are needed

198ff we believe there is no reason why a ATMP manufacturer should not have a standard quality system

259ff very valid point – e.g. mycoplasma testing with its 28 days duration may well exceed the shelf life of certain product

268ff agreed

284 ff agreed

293ff aseptic manipulation is prescribed to be carried out in A in a background of B and this is to ensure minimal contamination risks. The risk for contamination towards the patient is what it is regardless whether the product is minimally or otherwise manipulated and therefore we find it difficult to see why minimally manipulated products should require different/lesser settings. For reasons of practicality one might consider to allow e.g. mobile clean room spaces surrounding class A cabinets and to permit only a partial clean room cascade, e.g. black/B/A as long as this is technically feasible.

322ff we welcome the flexibility suggested to be permissible in early phase clinical testing. It would seem that the considerations laid out here also apply to minimally manipulated material as described earlier in lines 293ff and that the earlier paragraph should be identical to this one.

328ff a less than annual calibration, testing etc. of equipment does not seem to be advisable – its not a unusual burden on the manufacturer and it does help to ensure that processes run reliably. If a manufacturing process is carried out at a frequency lower than yearly it may stand to reason that other problems become more prevalent such as lack of routine, training and so forth.

336: specifications. Often ATMP processes require complex ingredients such as cell culture media. These typically lead to process termination if insufficient, e.g. a medium lacking certain critical components and hence we suggest to use successful process outcome as an important criterion.

368. the term “high standards” is unspecific and should be replaced by a more specific term, e.g. one may provide a brief explanation why hygiene is important in the manufacture of aseptic products and how it is provided.

We feel that this statement is an example of a less specific one than found in existing guidelines and hence may not provide an added benefit.

370ff -785

this section seems to be an abbreviated duplication of existing documents – we recommend against doing so.

804ff: “the level of documentation will vary”. It should be specified what is deemed acceptable

822ff a batch processing record. Is this intended to be synonymous with a batch record? If so we recommend to use the simpler wording to counter the inflationary use of terms sometimes seen in GMP contexts.

907 anatomical environment: is intended re e.g. the source of cell extractions?

1520: we feel this to be an important point

1548: 3 batches. The intent here seems to be to define what constitutes a small production volume. Batch sizes can vary from hundreds of ATMP products per batch down to 1 in case of autologous products; in the latter case 3 batches seems to be too small a number. We propose to use a product number or a statement such as production volume not to exceed that which is required for clinical studies phase I or II.

1624: very important statement!

2002: very important point!

With best regards,

Christian van den Bos

Dr. Christian van den Bos

Director / Mares Ltd.