**ATMP working group Netherlands & Belgium**

**Response to Consultation Document “Good Manufacturing Practice for Advanced Therapy Medicinal Products”**

General comments:

Since there is much overlap with existing GMP chapters and annexes, our working group would support a stakeholder meeting to discuss whether a stand-alone guideline for GMP for ATMP's or an annex to the existing GMP requirements would best address the needs of all involved stakeholders.

This document is generally written for ATMP containing cells. Although viral vectors are mentioned, most considerations and adjustments to the GMP as existing are related to the use of cells in the product.

| **Line** | **Current text** | **Proposal / Comment** |
| --- | --- | --- |
| 167 | operators | manufacturers |
| 203 | It is strongly encouraged that the advice of the competent authorities is sought for implementation of the risk based approach | Is this considered a GMP matter, hence should we reach out to our GMP inspectorate? Isn’t there a possibility that this will lead to different levels of acceptance in different member states? |
| 284 ev | With a view to avoid unnecessary administrative burden, in the application of the GMP requirements to ATMPs the manufacturing process of which does not involve substantial manipulation, account may be taken of equivalent standards that are applied by ATMP manufacturers in compliance with other legislative frameworks. | We are happy that flexibility with regard to non-substantial manipulation is included in this guideline.  However, it is not completely clear from this section and the sections below to what extend this flexibility is possible, i.e. does it also involve the release process or analytical testing? |
| 291 | However, premises/equipment used to process cells/tissues under the same surgical procedure derogation or for research purposes should be validated in accordance with these Guidelines | What is meant with “these Guidelines”? Please clarify.  We assume that these are the equivalent standards/other legislative framework. If not, request to remove this sentence as most operating theatres have not been designed nor built to meet Annex 1 requirements. |
| 299 | When manufacturing (…) in premises other than a critical room of grade A in a background clean area of grade B, a risk-analysis study should be conducted | Is this applicable only for ATMPs that are not subject to substantial manipulation or can this view be extended?  In general, exceptions to the requirements for premises are discussed in several sections in this documents which is confusing |
| 311 | QP release is an essential requirement applicable to all medicinal products, including authorized and investigational ATMPs the manufacturing of which does not involve substantial manipulation | This seems to be in contradiction with the text in line 284 and further. If production takes place in compliance with other legislative frameworks, then it should also be possible to perform the release according to these other guidelines. |
| 322 |  | exceptions to the requirements for premises are discussed in several sections in this documents which is confusing |
| 469 | materials from infected donors should be done in a segregated area. | Would this apply only to studies that target infected donors? There is an important difference in risk between working with HepB infected donors and the use of infectious viral vectors or HIV infected material.  We suggest to add “if necessary based on a risk assessment for the specific product” in order to allow for some flexibility. |
| 520 |  | exceptions to the requirements for premises are discussed in several sections in this documents which is confusing  Is the production process of viral vectors the only example for which these exceptions are allowed? Would it not be more clear to state that processes for which sterile filtration is possible can be performed A/C? |
| 542 | airflow direction | Does this truly mean that the airflow direction needs to be measured or can this information be derived from the difference in pressure between adjacent rooms? |
| 612 | Adjacent rooms of different grades should have a pressure differential of 10 – 15 Pa | According to Annex 1 these are guidance values. Suggestion to add’(guidance values)’ in the text, similar to Annex 1 |
| 614 | Negative pressure when infectious materials are used. | Would this then apply to materials that are known to be (routinely) infected? For exceptional infections it’s not practicable to invert the pressure cascades. |
| 765 | For autologous products, each unit should be considered a distinct batch. | If autologous products are used after reconstitution as described in section 16 of this document, then why couldn’t a batch consist of several (frozen) units? |
| 798 | A copy of the manufacturing order.. | Please define manufacturing order |
| 887 | This Section develops… | This section describes…? |
| 892  899  901 | Donor identification code (x3) | Error: should be ‘donation identification code’ (x3) |
| 1030 | The initial processing steps of the starting materials (*e.g.* isolation, purification) are manufacturing activities that should be conducted in accordance with the manufacturing requirements for pharmaceuticals, even if it is done by a third party (*e.g.* a tissue establishment). | This is a grey area where GMP and tissue bank authorities are sometimes contradicting, eg. regarding the GMP-status of the Clinimacs equipment. Please clarify.  Also, the term “manufacturing requirements for pharmaceuticals” is confusing. |
| 1186 | The compatibility of labels with XXX should be verified | There seems to be a word missing, eg. ‘actual processing and storage conditions’. |
| 1244 | For autologous products, there should be appropriate cleaning/decontamination between each batch. The cleaning/decontamination procedures should be validated (*see* Section 10.2). | This is somewhat confusing since it suggests that only for autologous products there should be appropriate cleaning/decontamination between each batch.  In addition, validation of cleaning/decontamination procedures with regard to autologous products needs additional explanation. |
| 1271 - 1274 | it is acceptable to conduct a manufacturing activity in a clean room which hosts an **incubator** which is used for a different batch/product if there is separated expulsion of exhausted air from the **isolator** and regular integrity checks of the **isolator**. | There seems to be a mix-up between ‘isolator’ and ‘incubator’. It currently doesn’t make sense… |
| 1326 | The integrity of the sterilized filter should be verified before use and should also be confirmed after use by an appropriate method | Filter integrity testing before use is not always possible, especially in the case of small scale batches where in line testing of filter is not feasible |
| 1342 | Simulation of reduced times for certain activities (e.g. centrifugation, incubation) should be justified having regard to the risk. | Isn’t everybody going to issue the same rationale for the incubator and the centrifuge, i.e. that the specific centrifugation/incubation time is not relevant with regard to the contamination risk? Isn’t it easier to simply accept not mimicking the full duration of these steps? |
| 1357 | A reduced frequency in cases of infrequent production may be justified. Thus, if the interval between the production of two batches is more than six months the process simulation test can be done just before the manufacturing of the second batch (three consecutive runs should be performed) | If three consecutive process simulations need to be performed before every batch, then this would result in more process simulations and therefore does not make sense (i.e. 1 batch per year would results in 3 process simulations, whereas in normal frequency, only 2 process simulations would need to be performed per year, i.e. 1/6 months (excluding the initial validation).  Propose to either remove this sentence or provide more explanation |
| 1461 | … in case of very small production | Please define ‘very small production’; Is this lots/year, units/lot or otherwise defined? |
| 1773 | Two-step release procedure: by the QP and by the sponsor. | For products with a very short shelf life (e.g. 2 hours), it is difficult enough to get a single release (by the QP) organized in the available timeframe, let alone introducing a second release. This is not practicable.  A solution could be to separate the release by the QP and the sponsor in time, i.e. have the sponsor release the application of the product for a specific trial based on the approval of the competent authorities, and have the QP release the individual products. |
| 1817 | Instances of administration of an out-of specification product to a clinical trial subject should be notified to the relevant competent authorities. | Each time or is it sufficient to report these instances on a yearly basis? |
| 2104 | The manufacturer should validate the reconstitution processes to be followed from the point of batch release to the moment of administration to the patient; | Presumably, process validation is not required for investigational ATMPs, analogous to section 10.3? |