Stakeholder consultation GMP-guideline for ATMP manufacturing

Reference: 2016\_06\_draft\_guideline, dd 23 June 2016-08-29

Collated comments from UZA CCRG, Antwerp, Belgium

| Line | Current text | Proposal / Comment |
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| 139 | Non-substantial amendments can be introduced in the IMPD without the agreement of the competent authorities | Would it be possible to illustrate this with a few examples of non-substantial amendments. |
| 203 | It is strongly encouraged that the advice of the competent authorities is sought wrt 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? |
| 291 | However, premises/equipment used to process cells/tissues under the same surgical procedure derogation3 or for research purposes should be validated in accordance with these Guidelines | Request to remove this sentence as it goes outside the scope of this document, ie GMP for ATMP manufacturing. Secondly, 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 296 grade B, a risk-analysis study should be conducted | So A in C can be acceptable, based on risk assessment.  Is this applicable only for ATMPs that are not subject to substantial manipulation or can this view be extended? |
| 311 | QP release is an essential requirement applicable to all medicinal products, including authorised and investigational ATMPs the manufacturing of which does not involve substantial manipulation | Request to remove the underlined part of the sentence as this is unpracticable: For many of these products there isn’t an available IMPD nor MA so the QP technically can’t release according to Annex 16. Also bone marrow that’s added to bone powder in the lab before being brought to the Operating theatre – in principle an ATMP without substantial manipulation – would now have to be produced under full GMP and QP released. |
| 387 | Clothing requirements: identical to Annex 1 | Goggles are not specifically mentionned, yet GMP auditors insist on us using them. The use of goggles creates additional operator fatigue and makes it more difficult to perform volumetric controls where reading of volume marks is required. |
| 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 infecteous viral vectors. Also the difference between ‘open’ and ‘functionally closed’ processing should be considered in both instances.  What is an infected donor? We suggest to limit this to HIV only. HIV+ patients are normally excluded, but we don’t see a reason to extend this to Hep and Syphilis. |
| 485, 542 | Requirement to control and monitor relative humidity | When is this deemed necessary? Humidity conditions are not defined for our products. |
| 506 | Production in a closed system or in an isolator: a background clean area of D grade is acceptable. | If systems are truly closed (maintain overpressure) then what is the relevance of this requirement? |
| 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 tekst, similar to Annex 1 |
| 614 | Negative pressure when infectuous materials are used. | Would this then apply to materials that are known to be (routinely) infected. For exceptional infections it’s not practivable to invert the pressure cascades. |
| 765 | For autologous products, each unit should be considered a distinct batch. | If autologues products could be used after reconstitution only as described in section 16 of this document, then why couldn’t a batch consist of several (frozen) units? |
| 889 | The manufacturer should ensure that the following data is retained for a minimum of 30 years. | Isn’t this duplication of cell and tissue bank legislation? Wouldn’t it be better to specify this in only one legislation? |
| 892  899  901 | Donor identification code (x3) | Error: should be ‘donation identification code’ (x3) |
| 994  1012 | The ATMP manufacturer should verify compliance of the supplier’s materials with the agreed specifications. Only released materials should be used… | Please include a remark that for fresh tissue/cell material not all test results may be available, esp microbial. |
| 954, 1169  1932 | Reliance on the certificate of analysis (…) | So it may be acceptable not to test samples of incoming materials? |
| 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. |
| 1186 | The compatibility of labels with XXX should be verified | There seems to be a word missing, eg ‘actual processing and storage conditions’. |
| 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… |
| 1275 | Simultaneous incubation/storage of different batches within the same incubator (…) evaluate possible risks and implement appropriate measures to avoid mix-up of materials. | Would colour-coding of autologues material be deemed sufficient? |
| 1277 | Closed vessel | How is this defined? Maintaining overpressure? |
| 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 recipients used are closed during those steps? Isn’t it easier to simply accept not mimicing the full duration of these steps? |
| 1365 | Matrix approach to media fill (…) based on identical handling of the product | If the handling is identical, then it’s one and the same process, so not really a matrix approach. |
| 1461 | … in case of very small production | Please define ‘very small production’; Is this lots/year, units/lot or otherwise defined? |
| 1464 | User Requirement Specification | To be issued retrospectively when not available? |
| 1653 | Safeguards to ensure that uncertified batches are not released should be in place | This is very hard to implement with ATMP that have ultra-short shelf-life eg 2hrs for DC vaccines, so half an hour between end of production and release by the QP; Doing anything extra in that timeframe seems difficult |
| 1773 | Two-step release procedure: by the QP and by the sponsor. | It is difficult enough to get a single release (by the QP) organised in the available timeframe, let alone introducing a second release. This is not practicable. |
| 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? |
| 1836 | In case of autologous products or donor-match situation, a control should be carried out to verify the match between the origin of the starting material and the recipient. | The control we perform is based on the lot numbering system we use that contains patient-ID. This lot number is documented at every step and verified a number of times. Is this deemed sufficient? |
| 1854 | General Principles (of sampling) | What if samples are very small volume and/or sterile? Can a potency test using a cell or tissue culture be an acceptable alternative for identity testing and full analysis? |
| 1856 | Bulk containers from which samples have been drawn should be identified. | In case of small or sterile containers they need to be disposed of after a sample has been taken, so what's the point in identifying them as they will no longer be used in production. |
| 2083 | Reconstitution of ATMP | All we do is thaw, wash, centrifuge, resuspend and adaptation of dose. This all falls under reconstitution according to the definition given. We welcome this new approach and will foresee the justification as requested, allowing us to step away from single dose batch certification by the QP. |
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