Advanced Therapy Treatment Centres

Northern Alliance Advanced Therapies Treatment Centre

# FAQ relating to areas of controversy around Manufacturing and Preparation of ATMPs'

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# Q&A for manufacturers detailing areas of controversy around

e.g. functional closure with agreed common solutions and best practice.

## 1. What are the expectations for minimising variant CJD risk in allogeneic products and is UK donor material acceptable for UK only clinical trials?

**Answer:** The regulatory expectation (as always) is that a risk based approach is utilised in all elements of GMP manufacture, and the minimisation of risk of exposure to prion agents is no exception (Annex 16 requires the QP to certify that a risk assessment has been performed with regard to prions).

There is a specific risk of transmission of variant Creutzfeldt-Jakob disease (vCJD) in the UK due to the epidemic of Bovine Spongiform Encephalopathy (BSE) in cattle in the 1980s which led to transmission through the food chain and the subsequent outbreak of vCJD, principally in the UK, but also to a lesser extent in Ireland, France and some other countries which received UK beef.

Of particular concern in vCJD is that prions are found in peripheral tissues including blood. It is known that vCJD prions can be transmitted by blood components and plasma products, 5 such transmissions have been reported all of which occurred prior to the introduction of universal leucodepletion in 1999. Whilst the outbreak of vCJD has now subsided, the number of people who may have subclinical, possibly transmissible, infection is uncertain. Broadly, international regulators have taken a precautionary stance and exclude blood or tissue donations from people who have spent more than a prescribed time in the UK (and in the case of the US, the rest of Europe). This includes the use of plasma for plasma product manufacture. However, within the UK, blood, cells, tissues and organs have continued to be used with no current evidence of further transmission since 1999, subsequent to which around 40 million blood components will have been transfused. Thus, whilst it is reasonable to use UK donors for donation of allogeneic starting materials for manufacture of ATMPs to be used in the UK, these are unlikely to be acceptable for products intended for clinical trial or adoption in other countries.

## 2. Is there scientific justification for not using sporicidal agents during the transfer disinfection of some components, common example is permeable blood bags?

**Answer:** The manufacture of ATMPs can often include a large number of manipulations, multiple days of manufacture, and incubation at close to body temperature in nutrient rich media. Each of these factors presents a risk for microbial contamination to occur and proliferate during the production process.
It is a fundamental principle of GMP that for aseptic manufacture (particularly where no terminal sterilisation process occurs), a robust and validated disinfection process is used. A disinfection process using only alcohol based agents will not be capable of eliminating the full spectrum of possible microbial contaminants including bacterial spores. The regulators expect that wherever possible, and unless scientifically justified, the disinfection process includes a sporicidal agent. Patients' starting materials are often procured into semi-permeable bags, there is a theoretical risk that the oxidising agents used for sporicidal disinfection could permeate these bags and adversely affect the cellular material (viability/karyology). Currently there are no robust scientific studies in the public domain scientific evaluating this. In addition, the evaluation of the impact of these agents must be relevant to the setting in which they are used. Critical factors include the agents used, contact time applied, method of removal of agent, material of the bag being used and whether it will be used as the final product container. NA-ATTC partners performed a validation of the use of sporicidal reagents for the transfer sanitisation of blood collection bags. The resulting report can be found in the Manufacturing and Preparation Toolbox on the ATTC website.

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## 3. When is rapid testing a regulatory expectation? Recently a European regulator insisted on rapid mycoplasma in addition to traditional mycoplasma on a fresh autologous product?

**Answer:** No single test in isolation can give absolute confidence in a product meeting specification. Quality assurance is the sum total of all the controls, rapid tests (if suitably validated and sensitive) can provide additional assurance when products are certified pending completion of all analytical tests. The value of adding in additional mitigations, such as rapid tests, should be commensurate to the likelihood and severity of the perceived risk.

## 4. What steps need to be taken when fully representative patient material cannot be used for process engineering / validation?

**Answer:** It is accepted that due to scarcity of material it may be necessary to validate using surrogate materials. When this approach is required it is important to consider the possible impact when defining the proposed specification in the Investigational Medicinal Product Dossier (IMPD) and also to closely evaluate and compare the analytical result from the initial clinical batches using patient material to data gathered during validation.

## 5. If the supernatant cell growth medium is capable of passing media growth promotion testing with BP organisms, can this medium be incubated post manufacture and used as a substitute for 6 month media fill tests?

**Answer:** The BP organisms are suggested as they give a wide variety of organism types, however no single medium will be capable of supporting the growth of all microbial contaminants. While it may be possible to validate a cell growth medium against the six BP organisms, if this was substituted for 6 monthly process validation it would almost certainly be subject to regulatory scrutiny. It may however provide useful information as part of a wider quality assurance strategy.

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## 6. When is it acceptable to use non-GMP raw materials and if GMP becomes available is there an expectation to re-validate using that material?

**Answer:** The principle of supplier approval is that the best quality materials should be used where possible. It is however accepted that within ATMP manufacture, particularly during the early phases, that there may not be GMP material available. In these circumstances, the company's supplier approval process should be applied to understand the potential risk and if any mitigations can be implemented, as such it may be possible to justify non-GMP materials. GMP manufacturers are required to apply the principles of continuous improvement and therefore should strive to introduce higher graded materials where possible; where material specifications are well defined and comparable it may not be necessary to re-validate in early phase clinical trials.

## 7. Are comparability studies required when QC samples are frozen in vials and product in larger bags?

**Answer:** While not being routinely requested by pharmaceutical assessors or GMP inspectors yet, it is best practice to recognise there can be difference in materials frozen and defrosted in different volumes and containers. It is important that QC results provide confidence that the product meets specification, as such a basic analytical study comparing viability and potency should be considered as a minimum.

## 8. When off the shelf systems (e.g. Prodigy tube sets, G-Rex) contain sterilising product and air filters, is there a need to integrity test these as defined in EudraLex - Volume 4 - Part 1 - Annex 1 - Good Manufacturing Practice (GMP) guidelines?

**Answer:** Annex 1 requires that bacterial retentive fluid and air filters that filter materials in direct product contact, are tested before and after use. Given the integration into the kits, it may be difficult to perform the integrity test before use without introducing some risk to product. In this circumstance, a risk assessment should be performed understanding what testing and assurance comes from the kit manufacturer, which may allow post use testing only.

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## 9. When filtration is being used to sterilise a non-sterile product or component, is double filtration the regulatory expectation?

**Answer:** Annex 1 states that consideration should be given for using two filters, when they are being used to sterilise materials. This is recommended but not an absolute requirement in phase 1 and 2 clinical trials.

## 10. What are the expectations for number and duration of storage of retention samples, do Annex 19 / 2001/20/EC expectations still apply?

**Answer:** When considering retention of samples, it is important to understand at what point the test, for which the sample was retained, no longer gives a representative result for the batch. For products with a very short shelf life or where there is insufficient product, a risk assessment should be performed to determine the appropriate sampling and retention strategy.

## 11. Is there a regulatory expectation to validate an in-use shelf life to allow for practical administration in a clinical setting (i.e. x hours after defrost / reconstitution)?

**Answer:** The requirement to do this is outside of the remit of pharmaceutical assessors and as such there is no regulatory barrier. However the NHS has an increased focus on 'undeliverable' products and as such for both commercial reasons and also to ensure the product has maximum clinical benefit it is sensible to do this.

## 12. Can Out of Specification (OOS) ATMPs be administered?

**Answer:** The administration of an out of specification (OOS) ATMP may be in the best interest of the patient, this depending on the nature and degree of non-compliance. Clarification of the regulatory perspective regarding OOS ATMPs for NHS organisations and about governance in the event of an OOS for ATMP being supplied to one of their patients is provided by the Pan UK Pharmacy Working Group for ATMPs **https://www.sps.nhs.uk/wp-content/uploads/2020/02/Out-of-Specification-Advanced-Therapy-Medicinal-Products-V1.2-March-2020.pdf**

## 13. When multiple patient collections are being processed on closed system cell processors simultaneously, what extra cleaning / measures to prevent cross contamination are expected?

**Answer:** It is possible to operate multiple cell processors within a single cleanroom; however, a robust risk assessment should be in place considering the failure modes that would allow cross contamination. These failure modes should be eliminated were possible, when there is residual risk after elimination or mitigation procedure and training should be in place to address the risk of cross contamination in the event of unplanned spills or aerosols being created etc.