The National Pharmaceutical Quality Assurance Committee is comprised of UK Regional QA Specialists who advise on technical and regulatory standards in relation to the preparation and manufacture of medicines. The group edits the standards required for unlicensed preparation services and ensure that they are upheld in the UK by externally auditing against the standards. The Committee has set up a Working Party for Advanced Therapies recognising that as they become more universally available – pharmacies and other NHS specialist cellular therapies colleagues will require advice re interpretation of the standards required for manufacture and preparation prior to administration. The Working Party Chair has therefore submitted this response on behalf of the National Pharmaceutical QA Committee.

The Committee do not agree with the stance regarding the need to reproduce a diluted form of GMP for ATMPs.

From a cell therapy manufacturer's or from a pharmacy's point of view this document is difficult to read in isolation without seeking clarification or detail from existing guidance (e.g. annex 1,2,13,15). As there is extensive guidance already available and cell therapy products are complex and highly variable from one product type to another it would be more useful to cite the existing annexes and then provide specific areas where problems are commonly encountered with cell therapy products. For cell therapy specific problem areas it would be useful to describe how deviation from existing standards can be justified based on the risk to the product and the patient to accommodate the unique challenges faced with cellular products. For example annex 1 is clear that continuous particulate monitoring is required throughout processing, it would be useful to understand if there are any exceptions for this for ATMPs given the necessity to use spray disinfectant techniques. If it is considered that the use of an isolator mitigates this necessity it would be ideal to state this as a suitable interpretation of annex 1 for ATMPs.

The Committee has not answered each question individually; our comments are mainly general due to the significant lack of detail in this document version- if this was intended as a standalone document we would have significant concerns regarding patient safety. In general it is our belief that as ATMPs are medicinal products then fundamentally they should be manufactured in line with GMP. Where, due to their specialist nature a degree of flexibility and interpretation of GMP is reasonably required then this document would be better to advise on how GMP should be interpreted for ATMPs, rather than trying to re-define GMP which has led to significant omissions. For example, it would be useful for individual standards within GMP to be referenced and then the allowable interpretation stated. This would then provide clarity for manufacturers and regulators and allow GMP inspections to continue to be meaningful. While phase 1 1st in human trials are considered to be IMPs there is no justification for reduced manufacturing standards, indeed it could be argued that these products pose the highest risk to patients and therefore should be the most tightly regulated. Academic research institutions are used to pre-clinical models and may not therefore prioritise patient safety. Hence advice guidance and regulations need to be clear on this. Rationale for our assessment that ATMPs are high risk includes the following points; sterile products susceptible to contamination in that they often have a protracted incubation period and are 'growing' in nutrient rich media and may have differentiated compared to their source cell type. They are not usually products that are suitable for terminal sterilisation, they are given to susceptible patients often using novel administration techniques, due to their mode of action they are retained or proliferate in the patient and are not eliminated in the same manner as small

molecule pharmaceuticals. These points lead us to want to encourage the highest standards of GMP during the lifecycle of the product.

The Committee recognise that there will be a new Clinical Trials Regulation being introduced into Europe, not earlier then 28th May 2016 and that this new regulation allows for some flexibility in relation to phase 1 studies. ATMPs used as IMPs should not be considered exceptional and should fall in line with the new clinical trials regulation. It may be useful for the GMP guidance to give an indication/examples of the required release specifications for ATIMPs during their development i.e. minimum specification requirements for Phase 1, 2, 3. This would then overtly encourage developers to begin to define potency and impurity assays etc at an earlier stage. QC testing is one of the significant omissions in this document.

In summary the guidance developed appears to conflict with the 'begin at the end'/ 'quality by design' methodology which we encourage within our healthcare setting remit. ATMPs are high risk medicinal products which should be manufactured according to GMP whilst recognising that some aspects of GMP may require specialist interpretation. The Committee would advocate that the GMP for advanced therapy medicinal products is amended significantly to signpost existing standards and provide the specialist interpretation required.

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