Dear Sir/Madam,

Below you will find our comments to Consultation document Good Manufacturing Practice for Advanced Therapy Medicinal Products, item 4.2.2 Aseptic environment; Answer to Q8 "*Should the use of a clean room with an A grade with a background of C or D grade be allowed for early phases of clinical trials (with the exception of gene therapy investigational medicinal products), provided that the specific risks are adequately controlled through the implementation of appropriate measures? Please substantiate your response. In particular, if you consider this option should be introduced, please address the benefits of introducing such flexibility and explain what measures could, in your view, be applied to avoid cross-contamination having regard to the potential risks (e.g. the level of cell manipulation, the use of processes that provide extraneous microbial contaminants the opportunity to grow, the ability of the product to withstand purification techniques designed to inactivate or remove adventitious viral contaminants, etc.)"* :

In the early phases of ATMP clinical trials we suggest and highly recommend that the work is conducted in A grade clean room with the C grade background or even lower grade. This suggestion is based on our experiences with the production of ATMPs. In the recent two years we have been conducting a clinical trial using the background of C grade. In this period we have developed and released more than 40 products, each of them was negative on both, the sterility test and test for the presence of endotoxins (performed in certified laboratories). The benefits of lower than B grade of clean room background (C or D) however are reflected in substantially lower cost (material, services, personnel), as well as saving valuable time. Moreover, the evaluation of risks/benefit scenario for patients indicates that setting up a B grade environment is not needed, since the safety and quality of ATMP products is ensured by the strict quality control -and also by taking into consideration the fact that the production is tailored to an individual patient. One patient one lot at the release. Hence, stringent quality control measures are adequate for the scale of operation, we have adopted. Furthermore, for small cell and tissue establishments, which represent the key driving force for development of ATMPs one has to consider the afore-mentioned experiences we have had, useful both for inspectors and also for the newcomers to the field.

In short, C grade working background together with the elevated measures in quality control represent a suitable measure to ensure quality and safety of the product, a manageable benefit-risk ratio to support more rapid development of new ATMPs for the benefit of un-met medical needs and is most suitable for early phases of clinical trials, as by the rule a small number of participants is involved.

The clinical trial that we are engaged in is a phase I/II (EudraCT: 2012-005498-29), in which we are collecting data regarding safety, immunologic and clinical efficacy of a cellular vaccine, consisting of hybridomas - fused dendritic and tumor cells. The production of hybridomas is a complex process, which takes several days and involves many phases (isolation of tumor and dendritic cells, freezing, thawing, fusion, maturation of cells, filling of injection with fused samples). Production phases take place in an aseptic environment with a grade A and with a background of grade C. All clean areas are formally validated and classified in accordance with a standard ISO 14644-1. Clean areas are also internally monitored for particulates (0.5 mm and 5 mm) and microorganisms in ''in operation'' state monthly, according to GMP recommendations Annex 1. Microorganisms are measured by air sampling (active and passive) and by sampling of surfaces and personnel. Personnel are regularly trained concerning handling with sterile products, personal hygiene and cleanliness. All exposed surfaces in lab premises are regularly cleaned by using prescribed sterile cleaning disinfectants.

Sincerely,

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PS Celica BIOMEDICAL is a Cell & Tissue Establishment