Swedish Association of Local Authorities and Regions (SALAR) - National Tissue Council
Swedish National Cell Therapy Group

Comments on 'Consultation Document – Good Manufacturing Practice for Advanced Therapy Medicinal Products'

The Swedish National Cell Therapy Group highly welcome the invitation for stakeholder comments on the EMA guidelines for ATMP manufacturing. Members of the group would like to take the opportunity to comment on the following questions and sections:

Q8 (p. 9): 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.)

Comment: A grade A room with a C or D background that is validated and used for early phase clinical trials could be acceptable if a risk analysis is performed combined with measurements of particle load and sterility test of final product. This reduction of current requirements could be done without increasing the risks for patients if routines are strict (i.e tissue directive). Furthermore, the modification in requirements would increase the probability of early clinical applications among EU researchers that is currently hampered by the strict GMP regulations for "low level" cell manipulation like culture expansion. The tissue engineering applications would thus easier come into clinical applications.

S**ection 16: Reconstitution of product after batch release** (p. 36).

Comment: We find it important that the transfer of a finally released product from the GMP production facility (such as for instance a cryopreserved cell product) into the clinical site of administration is not hampered by excessive demands on GMP laboratory requirements at the clinical site. Most clinical sites do not have class B rooms available for simple and standardized reconstitution of a product under GMP standards, and such a requirement could therefore pose a significant hindrance for bringing the product to the patients. In our case, we are planning for a cryopreserved stem cell product for transplantation to the brain,

and to increase the power of the clinical trial, we find it important that transplantations can be performed at several European clinical sites simultaneously. After delivery to the surgical site, the product requires thawing (using an automated thawing device), washing (i.e. dilution of the thawed cell product into a larger volume of buffered saline solution at room temperature), followed by centrifugation and resuspension prior to transplantation. We urge the commission to consider that such simple handling steps are classified as "reconstitution" and therefore do not require to be performed in a class B GMP facility.

Q25 (p. 36): How do you think that the GMP obligations should be adapted to the manufacture of ATMPs through the use of automated devices/systems? Who should be responsible for the quality thereof?

Comment: An automated system should be adopted to the GMP system and the responsibility for the quality should be divided between the manufacturer who should provide testing and approval of the automated system according to current regulations. Furthermore the producer should provide education program for the operating staff. The responsibility for the use and clinical validation of the product should be on the surgeon or doctor using the end product.

Respectfully and on behalf of the group,

Miriam Idar, Ph. D.
Project Manager

The members of the Swedish National Cell Therapy Group are:

Professor, M. D. Mikael Wiberg, Umeå University Hospital
Professor, M. D. Olle Korsgren, Uppsala University Hospital
Alexandra Karström, Uppsala University Hospital
Dr. Pontus Blomberg, Karolinska University Hospital
Professor, M. D. Katarina Le Blanc, Karolinska University Hospital
Dr. Gisela Helenius, Örebro University Hospital
Professor, M. D. Folke Sjöberg, University Hospital, Linköping
M. D. Stefan Scheding, University Hospital, Lund

Section 16 has been commented on by:
Associate Professor Gesine Paul-Visse, Dr. Agnete Kirkeby and professor Malin Parmar of the Neurology Clinic and Dept. Exp. Medical Sciences, Lund University, Sweden.