Devices that permit the selection and/or manipulation of cells are emerging. Often these devices are intended to be used in hospitals. The automated production of ATMPs through these devices poses specific challenges.

Q.25: 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?

PROPOSAL: The same GMP obligations adopted for ATMP manufacturing should be applied in case of production through the use of closed, automated systems. In this way, the main GMP objectives are ensured and therefore the overall quality of the product is safeguarded. Moreover, such closed, automated systems need to detect any process deviations potentially impacting on product quality and safety. Similarly, quality defects need to be identified as soon as possible and their origin has to be investigated and appropriate control measures have to be taken. A continuous process control approach is strongly encouraged, in order to detect any major and minor deviations which might affect the downstream product integrity, and all the different steps of such automated manufacturing process are recorded, stored and backed-up. As already recommended, a good documentation system has to be present to ensure that appropriate specification are laid down for the choice of starting and raw materials, to ensure product compliance independently form the manufacturing process itself.

In light of these requirements, if the manufacturer is able to ensure that the closed, automated device/system is able to produce, in hospitals, an autologous ATMP, as a finished product ready to be administrated to the patient, that:

1. is sterile (e.g. through both the use of sterile disposable elements contacting the biological material/ medicinal product -or any fluids in direct contact with them- and the design of a closed system)
2. contains an active drug substance for its intended use (cells, drug, proteins etc)
3. has not been subjected to cross-contamination or any environmental contamination (e.g. adventitious agents, leachables from disposable components used for manufacturing, pyrogens and endotoxins)
4. has been manufactured through a completely controlled and documented manufacturing system (including traceability), with appropriate process control points and validation methods

then it can be considered safe and effective in manufacturing an ATMP in compliance with current EU regulation and directives.

The automated device/system will ensure a high level of manufacturing quality in accordance with GMP rules, by automatically verifying that the relevant regulations governing the manufacture of

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medicinal products have been respected. Therefore we suggest that such a closed and completely controlled system may operate not only in a clean room of C or D grade but even out of it, in light of the minimal operator's intervention needed to operate the automated device/system.

Additionally, if such automated system is able to perform all the analyses required to assess the compliance to the established specifications, it is possible to avoid the intervention of the Qualified Person. In such case, the responsible for the product quality may be either directly the physician administering the ATMP or a trained person with a proper expertise and experience, not necessarily the same requirements currently stated for the qualified person.

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