

## **Setting minimum standards for the development and qualification of in-process and release QC assays for cell & gene therapies**

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Translation of cell and gene therapies from pre-clinical experiments to clinical trials and final drug licensing brings requires the development, verification and even validation of the assays essential for the definition of the drug product. The technical and scientific challenges in doing this are far greater than they seem at first and are compounded by a lack of approved standards for assays used to support (c)GMP manufacture.

ISCT has been championing the development and translation of cell & gene therapies for over 25 years and a staple of most ISCT annual meetings has been a flow cytometry workshop, often in partnership with ISAC. This reflects the central importance of flow cytometry and cell analysis to the products we are bringing into the clinic. No-one could imagine the development of a CAR-T cell therapy without a flow cytometer.

The challenge for the cell therapy field is to understand the complexity and limitations of flow cytometry as an analytical tool and to design the correct controls and validation data required to move from a research tool to a quality control instrument. ISAC has been here before with standardization working groups on CD4 enumeration and on leukemia and lymphoma diagnostics. Cell analysis assays will rarely achieve the level of reproducibility and reliable quantitation of the protein chemistry field which pharmacists are used to but we can at least set the same standards as we do for the use of flow cytometers and cell counters as diagnostic instruments and learn from that past experience. Moreover, it seems logical to apply the same standard to the therapeutic product as to the diagnostic tests which identified the patient as eligible for the therapy. This means that a list of target acceptance criteria for assays can be drawn up on the basis of the technical platform used; irrespective of the specific assay.

My GMP facility has been licensed by the two UK regulators since 2003 and we have experienced dual regulatory inspections roughly every 2 or 3 years. We understand the mindset of drug regulators and this has led us to develop ways of qualifying our flow cytometry and cell counting platforms to devise control strategies for operator dependence and to allow “intelligent” cluster analysis in flow plots. I will share our experience and propose some solutions I am working on with the UK MHRA, including new phenotyping panels for CAR-T and for MSC characterization and enumeration across multiple platforms from different equipment suppliers.