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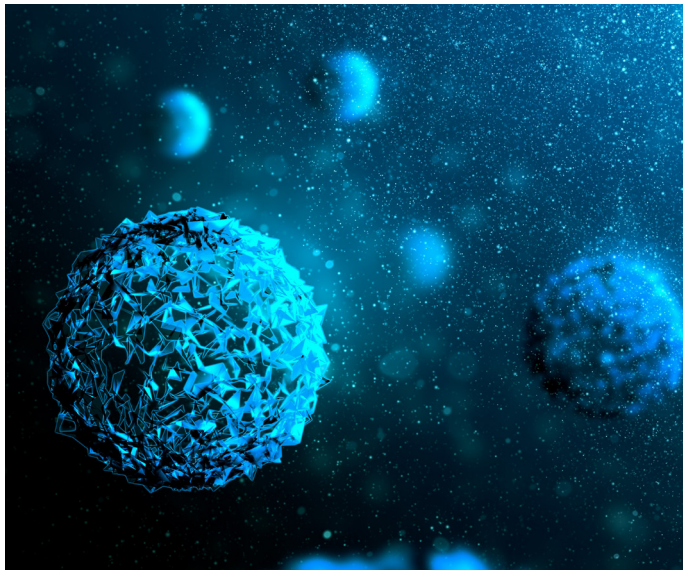
Quality control testing in CAR-T cell manufacture

Sagentia recently sponsored the Cell and Gene Therapy Strategy Meeting, held in Boston on 12th June 2018. Rob Morgan, VP Medical, chaired a round table discussion of quality control testing in CAR-T manufacturing focused on current challenges, the changing needs of emerging therapies and opportunities for the adoption of new technology.



A clear roadmap for the production and testing of CAR-T therapies will be vital for the stakeholders engaged in the delivery of these exciting new therapies in order to realize their full potential for patients.

CAR-T therapies are complex biological materials and because they are autologous they are inherently variable due to differences in sampled patient cell populations and their responses to processing. The production process is complex, requires high levels of operator skill and involves complex biological materials, not least the viral vectors used in genetic modification. Consequently, during the assessment of these therapies in the clinic, regulators have required an array of release tests to be performed on each single lot, single patient therapy. These release tests are required in order to show satisfactory identity, safety, purity and potency. CAR-T therapies have been shown to be highly effective in certain patient populations but also to have significant side effects, for example cytokine release syndrome, so the high burden of testing is understandable.

It remains to be seen how this testing burden can be reduced in production through additional process validation supported by greater sample numbers, but the logistical and economic burden of release testing can be expected to remain. In-process control testing is also required in order to manage the production of these personalised therapies and this places an additional burden on manufacturing.

The cost of CAR-T therapies is high – with Kymira priced at $475,000 per patient and Yescarta at $373,000 per patient - and the affordability equation will change as more therapies gain approval for wider patient populations. All contributing costs will require scrutiny, including the costs associated with quality control testing; both release testing and in-process control testing. QC testing cost estimates vary in the literature and the required testing varies with the stage of clinical development, but estimates given at the Boston strategy meeting were 10-20% of therapy cost.

Release testing contributes significantly to the timescales over which the CAR-T therapy can be manufactured and released for delivery to the patient, sometimes adding 100% on to the time from apheresis to formulation. Manufacturers will be under pressure to shorten manufacturing timescales and to do so by reducing the time needed for release testing.

Many trials are being sponsored by academic centers rather than commercial entities but a shift to commercial production is now occurring. Production will need to scale up in order to meet the population demands post market approval, new approvals will be granted and new patient populations will open up. A viable roadmap to CAR-T production at scale therefore needs to be understood and quality control testing is one part of this.

Some organizations are looking at decentralized models for CAR-T production for a variety of reasons. Commercial drivers include the ability to scale without individual players needing to invest in large, centralized production facilities. Logistical drivers include the need to service wide geographic regions with samples requiring low temperature shipping.

However, the move from GMP production under cleanroom conditions to multiple satellite locations, perhaps at the point of care in individual hospitals, brings significant manufacturing challenges – including the quality control of such production. Manufacturers and equipment suppliers are developing automation equipment for both centralized facilities and satellite locations. In each case the automation will ideally include more sophisticated in-line testing, reducing the need for sampling and manual transfer to off-line testing.

The landscape for CAR-T cell production will change as newer therapies gain marketing approval and as the regulatory framework adapts. Combination therapies – for example the use of CAR-Ts with checkpoint inhibitors - would place greater cost pressure on production.

New therapies with different antigen targets beyond CD19, using more precisely selected T cell populations beyond CD3+ and using different methods for transduction would change the quality control testing required.

Regulators are working with individual manufacturers to agree the quality control testing needed for individual therapies, and efforts are being made by regulators to provide more wide ranging guidance on release tests needed at Phase I, II and II clinical trials, as well as in commercial production. The regulatory framework will adapt as more information is collected by manufacturers on the critical quality attributes for the safety and efficacy of CAR-T therapies. In turn, testing technology will advance and evidence will be collected on how such critical quality attributes can be determined using faster and more cost effective methods.

Manufacturers will want to introduce new technology to release testing and at the Boston strategy meeting there was interest in using molecular biology based methods to both replace culture based sterility tests and to reduce the burden of culture based potency assays. Manufacturers will also want to use new technology for in-process control testing, for example cell identification tests based on flow cytometry principles.

Understanding the roadmap for future CAR-T cell production will be critical for the many stakeholders involved. Manufacturers, such as large pharmaceutical companies, biotech companies and contract manufacturers, will look to life science equipment providers and technology developers to solve the many remaining challenges of cell therapy production and quality control. Technology development can enable cost reduction, standardization and faster treatment, allowing wider patient populations to be treated as new therapies gain regulatory approval.

Dr Rob Morgan
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