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Manufacturing models permitting roll out/scale out of clinically led autologous cell therapies: regulatory and scientific challenges for comparability

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Abstract

Manufacturing of more-than-minimally manipulated autologous cell therapies presents a number of unique challenges driven by complex supply logistics and the need to scale out production to multiple manufacturing sites or near the patient within hospital settings. The existing regulatory structure in Europe and the United States imposes a requirement to establish and maintain comparability between sites. Under a single market authorization, this is likely to become an unsurmountable burden beyond two or three sites. Unless alternative manufacturing approaches can be found to bridge the regulatory challenge of comparability, realizing a sustainable and investable business model for affordable autologous cell therapy supply is likely to be extremely demanding. Without a proactive approach by the regulators to close this "translational gap," these products may not progress down the development pipeline, threatening patient accessibility to an increasing number of clinician-led autologous cellular therapies that are already demonstrating patient benefits. We propose three prospective manufacturing models for the scale out/roll out of more-than-minimally manipulated clinically led autologous cell therapy products and test their prospects for addressing the challenge of product comparability with a selected expert reference panel of US and UK thought leaders. This paper presents the perspectives and insights of the panel and identifies where operational, technological and scientific improvements should be prioritized. The main purpose of this report is to solicit feedback and seek input from key stakeholders active in the field of autologous cell therapy in establishing a consensus-based manufacturing approach that may permit the roll out of clinically led autologous cell therapies.

Key Words: *autologous cell therapy, comparability, GMP, manufacturing, point-of-care, scale-out*

Introduction

Recent analysis by Foley and Whitaker (1) has shown that an increasing number of clinician-led (i.e., clinical trials sponsored by an institution), predominantly autologous cellular therapies are demonstrating benefits to patients. Often involving complex routes of clinical intervention, these clinician-led therapies span those in which a degree of clinical adoption and proven efficacy already exists to those in which trials will be carried out under regulatory constraints more familiar with the regulatory route that industry-led cellular therapies must traverse (1).

Most companies seeking highly profitable business models work predominantly with scalable allogeneic therapies, following the traditional mass production biopharmaceutical manufacturing model as a route to market (1). Smaller-scale autologous therapies must follow alternative manufacturing and distribution approaches, dependent on the product (disease indication and prevalence), the method of preservation of the product and the fit with the systems in place at the final destination in the clinic (2). This may involve, for example, a central processing facility serving a number of clinical sites or a distributed model that requires localized processing within a hospital unit or manufacturing in-theatre or at the bedside through the use of closed or functionally closed automated processing systems.

The regulatory approach taken for specific autologous cell therapies is dictated by their intended clinical use, method of clinical delivery and manufacture. In some therapeutic cases, particularly in the orthopedic and cosmetic sectors, harvested cells are minimally manipulated (eg, by aseptic enrichment or separation techniques) and returned to the same patient. In most others, there is a requirement to expand the number of harvested cells in *in vitro* culture to generate a sufficient dose for therapeutic use. This expansion in culture, being considered by

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regulators to be more than minimal (or substantial) manipulation, raises considerable hurdles and challenges for both developers and regulators (3–6).

Manufacturing of more-than-minimally manipulated (MTMM) autologous cell-based therapies presents a number of specific challenges driven by complex supply logistics and the need to scale out (increasing the number of batches) production to multiple manufacturing sites or near to the patient within hospital settings. The existing regulatory structure in Europe and the United States sensibly imposes a requirement to establish and maintain comparability (demonstration of product equivalence) between sites.

At best, the assurance of comparability is achieved through a combination of *in vitro* studies, analytical testing and biological assays. Recently however, a consortium of stakeholders taking part in the Technology Strategy Board-funded Value Systems and Business Models project, known as "VALUE" (7,8), suggested that extensive safety testing of final cell product, while practical in the allogeneic setting, may not be feasible in the MTMM autologous setting. They concluded that because of restrictions related to small lot sizes, short shelf lives and the clinically limited time available for product and lot release testing it may not be possible to demonstrate comparability for additional manufacturing sites without costly and time-consuming confirmatory clinical qualification studies.

The cell therapy industry has experienced continued wrangling between regulators, lawmakers and practitioners and uncertainty as to the data required to establish quality, safety and efficacy of cell therapies (9–14), particularly with the International Society for Cell Therapy (ISCT) position on potency assays receiving recent attention (15). Against this backdrop, with point-of-care manufacturing not envisaged under current US and EU regulatory frameworks, with few MTMM autologous cell therapies on the market, for example, MACI (Genzyme), Provenge (Dendreon), ChondroCelect (Tigenix) and LaViv (Fibrocell Science), and with no precedent for a multi-site MTMM autologous cell therapy in Europe, it is clear that alternative cost-effective manufacturing approaches are required to permit the roll out of clinically led autologous cell therapies.

We propose three prospective manufacturing models for the scale out/roll out of MTMM, clinically led autologous cell therapy products, consider how they may be enabled and test their prospects for addressing the challenge of product comparability under the principles of the existing regulatory landscape. This paper presents the perspectives and insights of a small, selected expert reference panel of US and UK thought leaders from the industrial and regulatory community. It highlights the issues raised, identifies alternative manufacturing approaches, identifies where operational, technological and scientific improvements should be prioritized and where new enabling science is still required.

The regulatory challenge

Under the existing US and EU regulatory frameworks, cellular products that have been subject to more-than-minimal manipulation and/or do not carry out the same function in the recipient as the donor (non-homologous use) are broadly classified as either medicinal products (EU) or biologics (US), with relatively few regulatory distinctions made between autologous and allogeneic therapies and the characteristics that differentiate them (16,17).

In the autologous setting, the logistical hurdles associated with the clinically limited time available to transport harvested donor patient cells to the manufacturing or processing site and their return back to the clinical site for administration dictates both the manufacturing model (centralized versus distributed) and the clinical-site model (direct delivery versus clinical-site manipulation). This presents a number of ways of realizing the manufacturing/clinical supply process in multiple, distributed locations (Figure 1). The requirements for regulatory approval, Good Manufacturing Practice (GMP) and the level of validation relate, in part, to which sites are used for each element of the manufacturing and clinical process.

Manufacturers of autologous cell therapy products often introduce changes to manufacturing processes both during development and after market approval. Under the existing regulatory structure in Europe and the United States, when changes are made to a manufacturing process, the manufacturer is required to demonstrate comparability, that is, a demonstration of product equivalence before and after the change. This includes situations in which a second or reconfigured production line/unit, facility, location or supplier is brought on stream or when multiple sites of manufacture are introduced.

The scale out/transfer of manufacturing processes to multiple sites established before pivotal Phase III clinical trials (N model)[1] is probably achievable.

[1]The following model convention is used to differentiate the origin and scale of the potential routes for manufacturing roll out to multiple sites: Transfer of a product/process from an academic or hospital laboratory to a regulated manufacturing site (0+1 model); transfer to one or more additional manufacturing/production line(s) or to a regulated manufacturing location(s) within the same jurisdiction, either before (N model) or after Phase III clinical trials (N+1 model); transfer of product/process to regulated manufacturing site(s) within different jurisdictions (N+M model), that is, a site in each of the major geographical markets, transfer to 20 or 30 processing sites (eg, sites in international Centers of Excellence for major clinical specialisms) or transfer to 100 to 500 processing machine platforms, that is, systems "within a GMP setting" or "GMP in-a-box" systems (an example of true process scalability).

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