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GMP CAR-T cell production

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ABSTRACT

The clinical success achieved using CD19-directed CAR-T cells has stimulated many academic institutions to explore the feasibility of manufacturing these, and other CAR-T cells, in-house. This article reviews the issues that must be addressed in order to achieve this goal. It includes the manufacturing infrastructure, the regulatory environment, practical aspects of production, and the costs involved.

1. Introduction

For many years, cellular therapies have offered the promise of cure for a variety of diseases. Although some responses have been encouraging e.g. virus-specific T cells for prophylaxis and treatment of viral infections in immunosuppressed individuals, in the last 10 years the most impressive results have been achieved following administration of CAR-T cells to patients with leukemia. This has resulted in the licensure of CAR-T cell products by the Food and Drug Administration (FDA), and has stimulated investigators to explore the use of CAR-T cells to treat other malignant diseases [1]. These investigations will ultimately result in early phase clinical trials to evaluate safety and efficacy of new CAR-T cells. The FDA has mandated that these cells must be manufactured under an Investigational New Drug (IND) approval, and that the cells will be produced according to current Good Manufacturing Practices (GMP). GMP regulations provide a system by which the cells will be prepared under controlled, auditable, reproducible conditions that result in a safe, and potentially effective product. Many institutions are unfamiliar with these regulations and what level of compliance is required. An understanding of what is involved and the associated costs is essential to determine whether in-house manufacturing of CAR-T cells should be contemplated. The following sections highlight the issues that should be considered when making such a decision.

2. GMP regulations – what is required?

GMP regulations are found in various sections of Title 21 of the Code of Federal Regulations. They cover manufacturing of a variety of products, including foodstuffs, small molecule drugs etc. For CAR-T cells the most relevant sections are presented in Parts 210 and 211, with some additional information in Part 600. When read for the first time, the language appears somewhat unusual but, with practice, it is clear that “FDA speak” is designed to convey specific concepts, and understanding these will facilitate your interactions with the FDA. The comprehensive nature of the regulations is, at first, daunting, but a concise summary of what is required for manufacturing for early phase clinical trials is presented in an FDA Guidance “CGMP for

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Table 1
Main Areas addressed in FDA Guidance on CGMP for Phase 1 Investigational Drugs.

Area	Basic Requirements
Personnel	Adequate Education, Training, & appropriate Experience
QC Function	Written plan for QC that includes • Examining incoming materials • Review & approval of manufacturing & testing procedures • Product release/rejection • Investigating errors, complaints & deviations
Facility & Equipment	• Space, clean environment, appropriate construction • Appropriate lighting and HVAC • Appropriate equipment to maintain air cleanliness classification to prevent contamination/cross-contamination • Appropriate equipment that will not contaminate product and is properly maintained
Control of Components & Closures	• Written procedures for handling, review, acceptance & control of components, containers and closures • System to identify & trace all materials used in manufacturing • Acceptance criteria for the above
Manufacturing & Records	• Detailed record of manufacturing to include all reagents & equipment used • Record of product release or rejection • Record of any procedure changes • Record microbiological controls to include endotoxin
Laboratory Controls (Testing & Stability)	Scientifically sound testing procedures to include • Identity, strength, potency, purity & stability
Packaging, Labelling & Distributing	• Written procedures to cover packaging to protect alteration, contamination and damage • Tracking procedures for traceability, recall & complaints
Recordkeeping	Complete written records to include • Equipment maintenance & calibration • Product manufacturing & testing • Product distribution • QC Functions • Components • Deviations & Investigations • Complaints
Cell & Gene Therapy Specific issues	• Consider additional controls • Some recommendations may not be possible for these products • Monitor manufacturing performance to facilitate improvements • Conduct internal performance reviews to allow modifications and corrective actions

Phase 1 Investigational Drugs" [2]. The key areas discussed are shown in Table 1, which includes a special section that covers issues that relate to cell and gene therapy products.

Institutions that already have GMP facilities will be familiar with these regulations. Those that do not, will have to consider the cost of compliance and of building and maintaining the required space. Central to this is the anticipated volume of products to be manufactured, since a busy facility can break even, whereas one with excess capacity can be a considerable drain on resources, since it must be maintained even if there is no manufacturing taking place.

3. The facility

Once the decision has been made to build a facility, design questions become a major issue. A first decision is whether to use multidirectional or unidirectional flow of materials, waste, staff and products. This introduces questions about the potential for contamination and cross-contamination of products. Multidirectional flow uses the available space more efficiently, whereas in unidirectional flow designs the contamination risk is reduced, but a lot of space is required to create separate clean and dirty corridors. Plans can be submitted to the FDA to obtain feedback before construction starts. Recently CAR-T cell facilities that use the multidirectional model have received approval.

Air handling decisions become important when products may be produced for use in different countries. In the U.S.A. it is permissible to manufacture cellular therapy products in a Class 100 (International Standards Organization (ISO)-5) biological safety cabinet (BSC) located in a class 10,000 (ISO-7) room. In the European Union (EU) the BSC must be in a Class 1000 (ISO-6) room, which connects to a class 10,000 adjacent area.

Consideration must also be given to the manufacturing technique to be used. The trend is to move towards bioreactors to reduce the labor associated with traditional flask-based CAR-T cell production. Manufacturing in closed (or functionally closed) bioreactors should reduce the requirement for high classification rooms, since the risk of contamination is reduced. It is also possible, with the appropriate procedures in place, to locate several bioreactors in a single area. When manufacturing of multiple products occurs in one large room written changeover procedures must be in place to reduce the risk of product contamination and cross-contamination. With CAR-T cells cross-contamination can be detected using human leukocyte antigen (HLA) typing of the donor and CAR cells to ensure identity before product release (see later).

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