An Introduction to Phase-Appropriate cGMP Considerations for Cell and Gene Therapy

Readiness to begin GMP manufacturing is a decision point that requires careful consideration.

The first patient treated with any new drug is a significant milestone and achievement for every project team and individual champion of programs. This milestone is monitored closely within companies and their external stakeholders, shareholders and partner organizations, including contract development and manufacturing organizations (CDMOs). This is seen as a measure of progress in a journey which, more often than not, leads to "failure." Those failures do, however, provide the platforms for continued progression and the many successes we see in new drug approvals. In a landscape of such growth and impact of new technologies and new modalities, the decisions made along the way for these important steps represent the foundation being laid.

The continued recent increase in INDs for the newer therapeutic modalities of cell and gene therapies is well reported. The American Society of Gene and Cell Therapy with Informa Pharma Intelligence issue Quarterly Reports which provide encouraging and welcome updates on the state of this incredibly promising future for patients with significant unmet need. As of Q4 2021, there are reported to be eighty-nine cell, gene and RNA therapies approved and in clinical use, and 3,483 such therapies in development.[1] These Quarterly Reports[1,2,3,4] highlight over $3,340 million raised in seed and Series A financings during 2021 compared with $2,567 million in 2020, showing continued healthy progress in investment in these modalities. In the earlier stages of the pharmaceutical development lifecycle, as of January 2022, some 1,412 therapies are in preclinical stages with 248 formally in phase 1 and 244 in phase 2 of clinical development.[1]

As part of development and registration processes, helpful health authority designations are often available for these important medicines, including, but not limited to, Fast Track Status, Priority Review, Orphan Drug, Regenerative Medicine Advanced Therapy, or Rare Pediatric Disease. With these opportunities come expectations of agile and speedy development, not only by the sponsor companies but also regulators, patients and advocacy groups. The transition from research into early development and early clinical studies is an important one and a time when quality, compliance and the appropriate standards become essential elements of the programs. The readiness to begin GMP manufacturing is a decision point and one that requires careful consideration.

Those embarking on these steps come from a variety of starting points, including academic research labs, start-up companies and established mid-sized and larger biopharma companies, all sharing a desire to meet unmet patient needs but perhaps with different short- to medium-term goals and intentions for continued development of their precious assets. Regardless of the starting point, the questions often asked for early phase production are, "Are we ready to start GMP manufacture?" and "What is the appropriate cGMP for that manufacture?"

It may be surprising that this is often a debated subject in both small and larger companies. In the U.S., the debate is prompted directly by 21 CFR 210.2(c), which states, with some qualification, that the manufacture of an investigational drug for use in a phase 1 study is exempt from compliance with 21 CFR Part 211.

Figure 1. From Code of Federal Regulations, 21 CFR Part 210.2(c). "(c) An investigational drug for use in a phase 1 study, as described in § 312.21(a) of this chapter, is subject to the statutory requirements set forth in 21 U.S.C. 351(a)(2)(B). The production of such drug is exempt from compliance with the regulations in part 211 of this chapter."

However, clinical trial materials are subject to the statutory requirements of the Federal Food, Drug, and Cosmetic (FD&C) Act Section 501(a)(2)(b), which states that drugs and devices shall be deemed adulterated if they do not conform to current Good Manufacturing Practices.

Figure 2: From Federal FD&C Act 501(a)(2)(b)/21 U.S.C. 351(a)(2)(B) – Adulterated drugs and devices. "A drug or device shall be deemed to be adulterated… if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this chapter as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess."

Keith Lamb
Lachman Consultants

Keith Lamb, PhD is Executive Director at Lachman Consultants. He works primarily in Biologics and Cell and Gene Therapy and has over 30 years of Biopharma experience in Quality and Technical roles. He holds as PhD in Pharmaceutical Sciences from the University of Nottingham, UK, and a BSc Hons. in Microbiology from the University of Surrey, UK. He can be contacted at K.Lamb@lachmanconsultants.com.

> "A fresh eye with broad-based experience is often the quickest and most effective approach to establishing the capability to assess readiness and can be helpful to many organizations."

FDA's Guidance for Industry: CGMP for Phase I Investigational Drugs, published in 2008,[5] is an excellent document in providing context and direction as to what should be considered appropriate and aid to assisting with putting the right systems and procedures in place to ensure the appropriate application of current Good Manufacturing Practice to the manufacture of investigational drugs for use in phase 1.

Decisions to build new facilities, refurbish existing facilities or partner with CDMOs to support initial phase 1 studies may change during lifecycles. Swings in demand and available capacity will have an influence on such decisions. Experienced CDMOs will often bring established quality systems and have standards readily in place; however, the sponsor is encouraged, and required, to take accountability to ensure that the appropriate level of controls is established for the stage of development and further development of its asset. A fresh eye with broad-based experience is often the quickest and most effective approach to establishing the capability to assess readiness and can be helpful to many organizations.

As part of assessing what is phase-appropriate cGMP, the sponsor working with the manufacturer should consider the hazards associated with manufacturing the phase 1 material, as well as the context of the dosage form and drug, and document these and the assessment of risk, along with approaches to mitigation of those risks. Adequacy and clarity of procedures, along with control of equipment and the environment, are the bases with which cGMP is applied. Material and component inputs and sourcing may change over the lifecycle and should be appropriately controlled as some are critical. Also critical is the importance of the data generated, with accurate and consistent recording of manufacturing and testing data best achieved via application of data integrity principles. Strong consideration should be given to the understanding and application of ALCOA+/ALCOA CCEA principles via training and careful application.

As assessment of readiness is conducted when some commentary on a select number of exemplars provides a basis for the assessment. When considering the quality systems in place and in use, the roles and responsibilities of the quality unit, whether provided in an organized function or through consultant services and subject matter expertise, should be clear and documented. Appropriately experienced and trained personnel should carry out activities against procedures in place. Issued and controlled batch documents or procedures for GMP manufacture can be significantly tested and practiced through developmental and engineering runs. Critical quality systems, including management of change, deviation and CAPA, calibration, and maintenance programs, should be established and in use. The roles and accountabilities for these activities should be clear and documented.

The criticality of cell banks for gene therapy and other biological products warrants specific consideration. Viral and bacterial cell banks used to produce plasmid should be made under GMP conditions and have, at a minimum, a master cell bank (MCB) that is fully tested to regulatory standards for production and adventitious agents. Preparation of a working cell bank (WCB) to ensure continuity of production can be made later, and a comparability of the growth and productivity of the MCB and WCB can be established.

For progress through the development lifecycle, the processes for intermediates and plasmids should be characterized through phase 3 and validated. Specifications may be adjusted over time with process capability improvements; for example, a 2-5% range for host cell protein or host cell DNA at an earlier phase should be planned to be decreased to a more typical 1% level through process improvement or optimization.

Analytical methods qualified for use in establishing safety, identity, strength/potency, purity, and quality should be available for testing of phase 1 materials. Safety testing for adventitious agents and raw materials certified as TSE/BSE free must be used. Use of qualified assays continues in phase 2/3 and must be validated during phase 3 ahead of process validation. Commercial kits for residual host cell protein or residual host cell DNA may be used earlier in development but may need to be specifically developed for later in the lifecycle and commercialization. Analytical equipment should be qualified for the start of GMP testing.

Facility and manufacturing equipment should be planned to be qualified with a focus placed on manufacturing environment controls and key equipment. Design qualification is difficult to perform after the fact so, if the equipment and facilities are planned to be used beyond phase 1, it is best to complete such qualification in the design phase; at a minimum, equipment and facilities should be commissioned, calibrated, and maintained for the intended use. Use of single use equipment and components can simplify operations but careful management of sourcing and lead times is a must. Sterilization processes must be validated, and successful aseptic qualification runs completed, with operator training and qualification. Cleaning procedures and cleaning records must be in place, with cleaning validation required, as the product progresses towards commercialization. Computer systems must be qualified for their intended use with appropriate data integrity principles and controls in place.

Additional guidance and more extensive details are provided in the very helpful PDA Technical Report (No. 56, Revised 2016) titled Application of Phase-Appropriate Quality System and cGMP to the Development of Therapeutic Protein Drug Substance (API or Biological Active Substance).[6] **CP**

For a full list of refences visit the online version of this article at ContractPharma.com.

Note: Contributions were provided by Maureen Costello PhD, Senior Associate with Lachman Consultants.