How much is not enough, and how much is too much when developing quality systems and controls for investigational cell and gene therapies?

In an official statement in January 2019 by then FDA Commissioner Gottlieb, “the FDA is witnessing a surge of cell and gene therapy products entering early development, evidenced by a large upswing in the number of investigational new drug (IND) applications.” With new therapeutic modalities emerging in the cell and gene space (e.g., CAR-T and gene editing therapies) and their promising outcomes, companies are confronted with the need to quickly develop and test these therapies in clinical trials. Because these emerging therapies introduce biological material into human subjects for phase 1 trials, a scientifically based standard of controls and GMPs are required to ensure patient safety and assure Regulators that the Investigational Product conforms to the CMC information submitted in the IND.

As per 21CFR210.2(c), an investigational drug or biological product used in human phase 1 clinical studies is exempt from compliance with the GMP regulations specified in 21CFR211. However, these clinical trial materials are still subject to the adulteration clauses in the FD&C Act 501(a)(2)(b) that state that a drug is deemed adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not administered in conformity with cGMP. To help companies comply with the FD&C Act requirements, while considering the practical and risk-based exceptions to the 21CFR regulations, FDA published a Guidance for Industry for companies that manufacture phase 1 clinical trial materials. This guidance does not apply to “investigational products manufactured for phase 2 and 3 clinical trials (manufacture of such drugs must comply with appropriate sections of 21CFR211).”

Although, FDA has expressed support for regulatory flexibility for phase 1 manufacturing, reducing the GMP compliance burden during clinical development, and facilitating a faster route to early phase clinical studies. The use of phase appropriate GMPs and controls was never intended to provide firms an excuse to save money or cut corners; rather, they were disseminated to ensure basic safety and documentation standards are met in the manufacture and testing of phase 1 clinical trial material, and to encourage the design of quality into the process. It is expected that enhanced process controls and GMP
standards will be employed as the material transitions into later clinical stages.

To illustrate this point, I recently audited a viral vector manufacturer that was being qualified to manufacture and test viral vectors for phase 1 clinical trials. I was told that a production incubator used to expand the cells did not require qualification because the material produced was supporting phase 1 trials. While I am a fervent proponent of risk-based and phase-appropriate approaches to the application of GMPs and manufacturing/testing controls, I was surprised by this rebuttal since control over temperature and CO₂ are critical for optimal cell growth and viability. However, when I reviewed regulatory guidance and industry publications, I realized there could be different interpretations of the industry expectation to qualify critical process equipment. This requirement is outlined in the following guidance documents:

- **PDA Technical Report #56** – Application of Phase-Appropriate Quality System and cGMP to the Development of Therapeutic Protein Drug Substance, critical equipment should be qualified for its intended use for phase 1 manufacturing.
- **FDA Guidance for Industry** – cGMP for Phase 1 Investigational Drugs, the only statement about equipment qualification is that adequate equipment is used for the intended task and that it is properly maintained, calibrated, cleaned, and sanitized at appropriate intervals following written procedures. The guidance does not specifically call out requirements for qualification.

While my example is specific to equipment qualification, it illustrates a general point about defining controls and GMPs that are appropriate to the manufacturers of phase 1 clinical trial material. The basic components of a Quality Management System relevant to phase 1 manufacturing are detailed in the FDA Guidance for Industry; however, these controls are very broad and are open to interpretation. It is crucial that manufacturers of phase 1 clinical trial material assess potential risks associated with their manufacturing process, facilities, equipment, methods, materials, etc. and the associated impact of these risks on the safety and quality of the material. All significant risks should then be mitigated, and appropriate controls implemented to reduce potential adverse impact for the patients and data generated from the phase 1 study.

By establishing controls and implementing GMPs based on a documented assessment of risk to the patients undergoing treatment using cell and gene-based therapies, manufacturers of phase 1 material can relax some of the systems required for later phase and commercial manufacturing. However, this relaxing of standards should not be considered as a way to cut corners. Remember, these therapeutic treatments could be a life saving measure for patients enrolled in the clinical studies, and safety / efficacy of the treatment material must be the basis for all GMP programs and decisions.