Selecting and Qualifying a Regenerative Medicine CMO

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Among the most remarkable technical advances seen within the healthcare sector over the last decade is the fast growing sector of re- generative medicine. Breakthrough technologies are empowering re- generative medicine through the introduction of new, more accurate, easy-to-use tools and new drug therapies with the potential to be dis- ease modifying, capable of reversing the damage of certain diseases. It follows that adapting these novel processes to an outsourcing strategy requires careful consideration. Evaluating and selecting a contract manufacturing organization (CMO) is one of the seminal decisions that can influence the overall success of a development program. This article will discuss a recent case study using human cells, tissues, and cellular and tissue-based products (HCT/Ps) that are regulated by the Center for Devices and Radiological Health (CDRH) as medical devices and those that are regulated by the Center for Biologics Evaluation and Research (CBER).

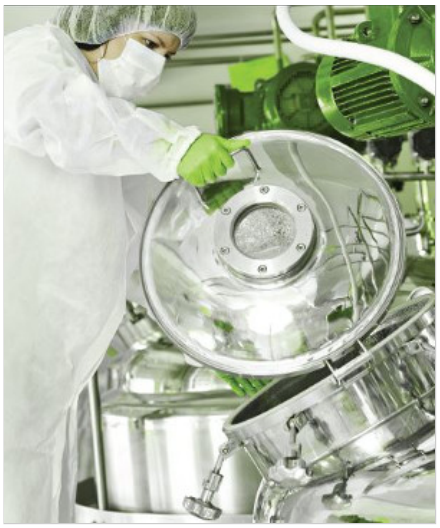
A U.S.-based drug sponsor has been manufacturing multiple HCT/Ps under a regenerative medicine advanced therapy (RMAT) designation by the FDA. The RMAT designation was created as part of the 21st Century Cures Act. A drug is eligible for RMAT designation if:

a. The drug is a regenerative medicine therapy, which is defined as a cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products, except for those regulated solely under Section 361 of the Public Health Service Act (PHSA) and part 1271 of Title 21, Code of Federal Regulations;
b. The drug is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition; and
c. Preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such a disease or condition.

Project Background

The FDA has informed manufacturers, healthcare providers, and other interested persons that by the end of 2020, the FDA intends to exercise enforcement discretion under limited conditions with respect to the investigational new drug (IND) application and premarket approval (biologics license application (BLA)) requirements, for certain HCT/ Ps. This will migrate drugs currently regulated under 21 CFR 1271 and Section 361 of the PHSA to Section 351 of the PHSA that reflects the current regulatory framework for biologic drugs.

For drug manufacturers currently supporting RMAT



designation products regulated under Good Tissue Practices (GTP), the transformation and implementation to full drug GMPs is a significant task. To that end many drug sponsors find themselves evaluating an outsourcing strategy in parallel with their in-house GMP readiness activities. This was the case with the drug sponsor we discuss here.

CMO Evaluation and Selection

The evaluation criteria for a regenerative medicine CMO are not markedly different from a small or large molecule product: however the technology transfer and readiness challenges can be exacerbated depending upon the FDA's regulatory review. If the proposed therapeutic indication addresses an unmet medical need or is granted breakthrough drug status it is likely that the product may be allowed to skip early clinical testing and move to pivotal studies right away, placing significant pressure on the quality and CMC elements of the program to be ready with final parameters, specifications, methods, etc. in time to support the regulatory timeline. This was the situation for the drug sponsor in the present case study.

Technology Transfer

Transferring a process and product developed under GTPs to a CMO grounded in GMPs has myriad challenges. The following are considerations to make when developing criteria for evaluation of a potentially viable contract services partner:

Characterization and Analytical Testing

HCT/Ps approved under the RMAT designation are approved for a mode of action, such as anti-inflammatory or anti-scarring rather than a specific disease state therapy. There is no division between the regulatory starting material (RSM), drug substance (DS), and drug product (DP). This can be confusing for experienced CMOs that have supported small molecule or large molecule biologic products. Products that do not have a direct linkage to a drug substance and its characteristics that drive the therapeutic mode of action utilize a matrix approach of analytical tests. Seeking out CMOs that have experience with bioassays as a surrogate for potency testing is important if the CMO is to do incoming quality assurance testing, in-process, or release testing.

Establishing a framework for evaluation is also recommended when meeting with the product sponsor's technical team, as they are likely the personnel with extensive knowledge of the product and process development, albeit in the context of meeting the characterization demands of an RMAT product. Summarizing all relevant product and process development and characterization studies must be included in formalized developmental reports that provide a snapshot of the recent history (e.g. known issues, process and design space, effects of material attributes, etc.) will be very useful when trying to agree upon a final control strategy to communicate to the CMO.

It is possible that the CMO will have little or no experience with some of the unique and complex analytical methodologies used as part of the potency matrix and stability testing. Because of the inherent variability due to donor variation in the raw material, method transfer can be a daunting undertaking. A stepwise program which establishes a robust database of the finalized analytical methods at the drug sponsor site is recommended before attempting to transfer the more complex assays associated with the potency assay. Compendial or standard analytical methods can be transferred to competent third parties with relative ease, but product specific analytical methods for regenerative medicines can be quite complex and highly technical procedures that reside on the cutting edge of science. These methods must either be retained with the sponsor or outsourced to competent third-party labs if scale and throughput is a concern. A firm understanding of the CMO's analytical testing ability including the technical foundation for the assay as it relates to the drug

therapy's mode of action or quality sensibility, methodological competence, and equipment are critical to the successful transfer of methods necessary for testing in-process and release material.

Product and Process Knowledge

Establishing a Target Product Profile (TPP) and Quality Target Product Profile (QTPP) is essential to beginning the process characterization discussion and for initiating the paradigm shift within the development and quality organization to a BLA framework, as this will set the stage for populating the final control strategy. A structured Quality Risk Management (QRM) process will define the potential impact of proposed CQAs on each unit operation. Even if the measurement tools are esoteric the process development and measurement criteria can be clearly explained to a CMO. Although the fundamental RSM is harvested, rather than synthesized or manufactured, there is downstream processing of the material to prepare it for commercial scale manufacturing. Scale-down models can be used to establish a process design space, as with large molecule drugs.

One challenge when establishing the User Requirements for a prospective CMO is managing the dichotomy between human tissue processing and conventional large molecule processing. While there could be overlap between the PHSA Section 315 and 316 regulated processes such as Master Cell and Working cell bank validation, the processing steps for human tissue can be very specific to the product mode of action. Simple challenges such as providing a Safety Data Sheet (SDS) for material to be processed - which is a minimum prerequisite for any CMO to receive material - can take some brainstorming to satisfy. If the CMO has previous experience with processing tissue they may not have experience with final processing steps, such as fill finish, and vice-versa. Bridging the requirements as specified by the American Association of Tissue Banks (AATB) and the FDA's 21 CFR 600 requires a clear understanding from a CMC perspective as to how the product's ultimate mode of action will be described. The new guidance on HCT/Ps allows both Section 361 and 351 standards to apply to different stages of the process which can further complicate technology transfer discussions with a CMO. Having these discussions early in the evaluation process is essential to selecting a CMO partner that will be able to support you as the program moves to developing the required information to support a BLA.

The goal (and primary indicator) of a successful technology transfer is the characterization of the final process capability and rigorous application of suitable controls that preserve the critical to quality attributes. The ideal outcome is a process that can be controlled parametrically and provides a high degree of assurance that the in-process controls guarantee a quality product.

Facilities and Equipment

From a regulatory perspective, facilities and equipment must be appropriate to their intended use. Technically, however, a transfer is most effective with a CMO that has prior experience with similar products. For sponsors on the bleeding edge of modern regenerative medicine it can be considerably difficult to find the "unicorn" that manufactures similar products, fits the necessary capacity, and is well-equipped to meet the product's handling and processing constraints.

Leading edge drug development is often an iterative conversation between the FDA and the drug sponsor. Leveraging the Written- Response-Only (WRO) process is essential post IND to making sure the agency's assumptions and expectations are clear and the drug sponsor's strategy for demonstrating compliance is appropriately matched. Often this requires a CMO partner that is willing to participate in the problem- solving exercise as they may have to adapt their current systems to accommodate the processing of the HCT/P. In many cases, the receiving site will be "nearly" capable, but additional equipment or training is necessary. Whether a product is aseptically processed or terminally sterilized greatly impacts these requirements. For products processed aseptically, air handling, cleanroom cascades, biological safety cabinets, and supportive material (i.e. gowning and tools), must meet product requirements for sterile or aseptic handling. The final physical form of the tissue product can reduce the potential list of CMOs capable of accommodating the unique elements of tissue processing. Plan for the relevant equipment and environmental

qualifications, improvement of cleaning methods, and all training necessary to fit the product and

the personnel safety assurance levels.

Quality Systems

Effective quality systems, in tandem with the concept of Quality by Design (QbD), form a fully compliant basis for transitioning a product from development to commercial phases and beyond. An effective quality system is one that enables and governs activities informed by fundamental science and risk-based approaches to build safety, quality, identity, purity, and potency into the product regardless of, but assessing, input material or manufacturing variability. For sophisticated regenerative medicine products and their complex manufacturing processes this is even more critical than for small molecules and traditional biologics.

Both the initial transfer and all subsequent manufacturing operations must be firmly integrated with QMS between the sponsor and the CMO. Technical and project management, oversight, and review of work products are particularly critical to meeting regulatory and business requirements such as material and supplier qualification, implementation and enforcement of the control strategy, and continuous process improvement. Many CMOs are already manufacturing biologics or small molecules under CGMP and may have effective systems to support regenerative medicines in place. However, a careful review of regulatory history and on-site audits will further indicate their capabilities for the specific requirements of innovative and biologically intricate products. Although the capability of a CMO's quality systems must be part of the initial evaluation and selection process, many details are finalized through a formal agreement regarding communication, roles, and responsibilities for quality, operations, engineering, medical, supply chain, and analytical departments. Successful integration of quality systems and mutual understanding of QbD between the sending and receiving sites are critical to avoiding and overcoming any issues for technology transfer programs.

Conclusion

Identifying a suitable CMO partner capable of supporting the transition from RMAT designated product programs to a fully approved BLA will require the drug sponsor to anticipate and bridge the current assumptions of both regulatory frameworks. The promise of this class of products to address unmet medical needs is immense. To be successful, not only will the drug sponsor need to apply the key evaluation criteria for managing a conventional small or large molecule CMO, such as RACI1 frameworks in their development agreements, but also provide context for the CMO to understand the basis for the process and product design, testing, and release of the product.

References

1. https://en.wikipedia.org/wiki/Responsibility_assignment_matrix

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