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INTEGRATION OF MANUFACTURING & DELIVERY INTO HEALTHCARE

SPOTLIGHT

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An Industry Perspective on the Clinical Preparation of Cell Therapies

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Cell therapies are a promising class of biologics which exhibit many capabilities not available to other pharmaceuticals. Cells can respond to their environment in a conditional and multifunctional manner, and in some cases can home to specific regions or proliferate within the patient. These unique properties enable new therapeutic approaches to treat patients' unmet medical needs. However, there are also new challenges that extend all the way to the patient's bedside. With a medicinal product that is alive, the delivery and administration procedures must be designed and controlled to ensure cellular health, while also managing the complexity and biological limitations of specific cell types. As a practical matter, solutions must align with existing medical infrastructure to get viable drug products to the patient populations who need it. From an industry perspective, the goals around clinical preparation and administration are to provide a safe and effective therapy in a standardized manner that is operationally efficient and robust.

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Cell therapy manufacturers want to make the best possible products for customers: pharmacies, prescribers, and patients. The clinical preparation and administration procedures are a critical step in treating patients and proper development of these procedures is essential for technical, regulatory and consumer needs. The preparation procedure should be designed, controlled and demonstrated to yield consistent and reliable final product. Where possible, manufacturers should put systems in place to minimize burdens on the clinic. This allows a better customer experience and greater assurance the drug is prepared as intended.

DETERMINING PRODUCT PREPARATION OPTIONS

The strategy for product preparation is influenced by many factors including patient needs, product constraints, practitioner preferences, clinical trial requirements (e.g., blinding), regulatory requirements, release considerations, and an ultimate desire

to commercialize. Those diverse influences largely prevent a one-size-fits-all solution, but they also provide a logical framework for decision making. Depending on the therapeutic hypothesis and the treatment, some options will be favorable, unfavorable, or infeasible. Clinical preparation for a product which is surgically implanted in the brain will be very different than that requiring an intramuscular injection administered by a visiting nurse in a patient's home. These considerations and constraints are integral to forming a Target Product Profile (TPP), which ultimately shapes many clinical preparation decisions.

The TPP frames the vision for the product. What are the cells meant to do, and how are they administered? Where are patients treated, how do they present, and what are their needs? What sort of medical practitioner uses the product, and is the product preparation within the scope of their training and license? How are the cells made and distributed? Collectively, the answers to these questions form the boundaries of available options and set up the grounds for trade-off decisions. Those decisions can be built into the TPP or a set of possible TPPs with base, optimistic, and conservative options.

Some therapies have specific demands based on the patients' needs or the cells' capabilities. For example, an acute condition like ischemic stroke may need product administered within a narrow time window. This might mandate a locally stored, cryopreserved product if there is not sufficient time to arrange a shipment. Furthermore, cells also have limitations; some cell types can be cryopreserved, while others suffer severe loss of viability or function on freezing.

An example of a common trade-off with cell therapies is the use of cryopreservation for allogeneic cell therapies. Most allogeneic therapies use an unmatched donor, and allow for one donor to be given to many patients. This model supports scale-up into the tens to thousands of doses per production batch, and yields many of the same benefits of scale as traditional biologics: more efficient production, a stable window for release testing, reduction of cost of goods and improved ability to characterize each donor and lot. However, the decision to cryopreserve means cells must be thawed and typically prepared on-site, which puts additional effort and burden on the clinic.

DEVELOP & OPTIMIZE THE PRODUCT PREPARATION PROCEDURE

The goal of preparation and administration procedures is to provide a safe and effective therapy in a standardized manner that is operationally efficient and robust. If there are parameters in the procedure that could affect product quality, they must be controlled through design, procedural controls, and training. The challenge is not just to ensure that procedures are understood and implemented, but also to find scalable and simple solutions. As studies progress to larger trials and commercialization, it becomes harder to ensure appropriate handling at every site. The best approach is to design a procedure that is robust and insensitive to operating parameters, to focus on creating a "low effort" procedure with fewer opportunities for

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error, and to be systematic and thorough in training.

Design of the preparation procedure requires product knowledge and process understanding of putative failure modes. The approach to identification of critical parameters and characterization of their effects on critical quality attributes is very similar to the development and validation of drug substance and drug product processes. It requires careful consideration of potential failure modes and testing with sensitive assays. Once there is a good understanding of how product failures may occur, whether from inadequate control of sensitive parameters or from potential errors, the procedures should be written carefully to reflect those priorities.

Consider a relatively simple three-step procedure in which a frozen vial of cells is thawed in a water bath, gently mixed, and then filled into three syringes for injection. Where might it fail? The product may be sensitive to thaw rates. Cell culture best practices suggest transferring the frozen vial into a pre-warmed environment quickly to enable a "rapid thaw". The rapid thaw limits the ability of intracellular ice crystals to ripen and grow during warming. Is this a theoretical concern or a real sensitivity? Manufacturers should evaluate the risk for their own formulation, freeze process, and cell type. There may be scenarios where the product is overheated. If the procedure calls for a 5-minute thaw in a water bath, what is the product impact if the pharmacist gets an urgent phone call during the thaw and the vial is warmed for an extra 10 minutes?

Mixing is an important post-thaw step to resuspend any settled cells and to eliminate any DMSO gradients caused by phase separation during freeze–thaw. However, there can be substantial operator interpretation in how mixing is accomplished. An instruction to "gently invert vial five times to mix cells" might be carried out over the course of 5 seconds at one site or over a minute at another. Is there adequate mixing? Does the shear from mixing damage cells or introduce air bubbles?

In the final step of this procedure cells are drawn into a syringe. Does it matter how fast the cells are drawn into the syringe, or what size needle is used? It is up to the manufacturer to assess the sensitivity of the product and to determine whether it needs to be better controlled.

In some cases sensitivities can be eliminated with process changes to the formulation or upstream process, but often there are limitations which just need to be controlled. Most cell types have limited stability in their final formulation, beyond which viability or function are compromised. Some stability issues can be addressed with additional formulation development, but it's usually necessary to set formal expiry times to control the procedure. Another common behavior is cell settling. In some cases, the settling may be in a vial which can be inverted or a bag which can be massaged. Settling in small bore syringes is harder to deal with, and it may be appropriate to set an expiry limit based on cells settling and sticking to walls rather than cell health or function.

PARTNER WITH MEDICAL PROFESSIONALS & PROVIDE APPROPRIATE TRAINING

In the course of our work, we've trained hundreds of medical

professionals on the preparation of cell products, including nurses, pharmacists, physicians, and medical technicians. The individuals have worked in pharmacies, blood banks, outpatient offices and stem cell laboratories. They have had a broad diversity of knowledge and experience, from people who had never seen a cryogenic dry shipper or prepared a cell therapy before, to people who had prepared hundreds of investigational products and were rightly regarded as experts in the field. In all cases, our reason for conducting the training was the same: we believe that how a product is handled is important to the safety and efficacy of the product, and to patient care.

Training is important for all but the simplest of procedures, and becomes more critical for longer or more sensitive processes. The training program should align with and support the written procedures, and it should cover how the product is received, processed, documented, and disposed. It should discuss appropriate Personal Protective Equipment and any material safety information related to the product. It may include key safety issues such as off-gassing of dry shippers and instruction to keep them in well ventilated areas.

If there are known product sensitivities, they should be emphasized and explained. Suppose a cryopreserved product needs a rapid thaw to prevent re-crystallization damage during warming. The procedure should have a boldly emphasized instruction to remove the unit from the cold environment and proceed to thaw immediately. The training should go beyond what is written in the procedure, by contextualizing "immediate" and explaining why it is important. Should the step be completed in 30 seconds, or is it more like 60 or 90 seconds? The procedure should be consistent with the needs. If the thaw timing is sensitive, don't have the preparer confirm the product label until after the thaw. If the thaw is timed, set up the written procedure so the timer is already prepared. If you want special attention on critical steps, include why the step is critical as part of training. A short discussion of how rapid thawing prevents cell death and damage from growth of intra-cellular ice crystals gives additional context to the step and helps reinforce understanding and retention.

The priority and extent of training efforts should be consistent with the complexity of the preparation process and the sensitivity of the product to handling. Longer procedures require longer training and have more opportunities for errors. Consider whether this warrants multiple instances of training, a proficiency evaluation or other solutions. For fairly simple procedures it may be acceptable to train one individual and allow them to train back-ups or replacements. For more complex procedures it may be necessary to train each individual. Consider issuing certifications as an acknowledgement of trainees' attention and diligence.

The format and scalability of training are also important. In early development it may be worth conducting training in person. Training 1-on-1 has many advantages; for one thing, it shows the sponsor's commitment to the product and the training effort. It also allows trainers to better identify with customers and understand

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their needs. Finally, it's also a great time to solicit feedback on the procedure itself. As the product progresses through development to commercialization it becomes less feasible to attend every training in person. Consider more scalable options, such as a training video, or interactive web meeting.

Practice is another element of training and is valuable for both understanding and retention. Mock shipments or training runs can help make both parties more comfortable with the procedure. Most people don't find it easy to pull a vial out of a dry shipper with giant blue cryogloves on, especially if they've never worked with a dry shipper before. Knowledge retention can be an issue if it's a long time between patient doses. Consider periodic refresher training if a scalable option has been implemented.

Last but not least, training works best as a partnership. Of course we want sites to feel comfortable with the trainers, and to know that they can reach out anytime they have questions. Questions are never stupid: they help us understand what has not been sufficiently explained. Suggestions are even more valuable. Many of our best procedural and training solutions were prompted by site feedback.

LOOK FOR OPPORTUNITIES TO INNOVATE & STANDARDIZE

Cell therapies are typically developed in cell culture laboratories, and most product preparation procedures use equipment found in a cell culture lab: water baths, biosafety cabinets, and centrifuges. This type of equipment is versatile, functional, and well-tested in a laboratory setting, but has some drawbacks for product preparation in a clinical setting. Water baths take time to warm and need to be managed properly to prevent incubated growth of microorganisms. Biosafety cabinets are expensive and have a large footprint. They may be distant and inconvenient in large hospitals, or not available in smaller clinics. Centrifuges have similar issues. As cell therapies become more prevalent, it's likely there will be more specific tools and methods for product preparation.

One example is the use of dry thaw equipment to replace water baths. These units are able to uniformly apply heat to frozen vials at a rate nearly identical to water baths, but with less warm-up time, better control over the specific thaw cycle, and no risk of waterborne contaminants. Celgene Cellular Therapeutics recently implemented the ThawSTAR® Automated Cell Thawing System (BioCision, USA) in one of our PDA-002 trials. The equipment is designed to have a small footprint and is extremely simple to operate. It initiates the thawing program cycle when a frozen 6 mL vial is inserted and the thermal contact block engages. The thaw cycle begins and thaws the vial for about 9 minutes, similar to a 37°C water bath. Once the cycle is completed, the vial is released and can be removed from the instrument. Empirical data for PDA-002 showed the thaw profiles were very similar to a water bath and the cell health and function were equivalent. Use of the ThawSTAR® simplified the clinical procedure, reduced the opportunity for errors, and received positive feedback from the pharmacists in the trial.

CONCLUSIONS

As we seek to harness the potential of cells, we must also manage the intrinsic complexity of cells, and ensure proper care of these living drug products. Product preparation at the clinical site should be designed around the product profile, then developed and optimized for the specific treatment setting. Manufacturers should focus on creating a "low-effort" experience for customers, and partner with them on training needs to ensure product quality. As the field advances, there are opportunities for innovative solutions to clinical preparation issues, and possibly specialized administration centers.

FINANCIAL & COMPETING INTERESTS DISCLOSURE

The author is an employee of Celgene Therapeutics. The author has no relevant financial involvement with an organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock options or ownership, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.

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