DARK HORSE CONSULTING

CASE STUDIES

Accelerating cell and gene therapies through unmatched expertise

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Interim Functional Leadership

Why DHC?

- Expand Client Bandwidth
- Provide Additional Technical Expertise
- Solve Existing Problem (Remediate)

The Ask

DHC has encountered a variety of examples in which a client requires a temporary personnel solution, a sort of strategically savvy SME-on-demand, and the approach we take to those varying situations can differ.

Senior leaders at DHC have held leadership positions at numerous companies in the past. Because our experts continuously collaborate on projects for gene, gene-modified, and cell therapies across multiple modalities, encompassing all stages of development (nonclinical through to commercial), we're uniquely equipped to provide as much or as little support as any given situation requires.

This support could be in the form of leadership (Chief Technology, Manufacturing, or Regulatory Officer) or technical expertise in the areas of CMC, manufacturing, quality, regulatory, analytical, non-clinical, project management, and/or regulatory writing.

Service Domains

DHC's Approach

Our teams can take a hands-on, daily embedded approach or act as strategic advisors taking an outside-in approach. Occasionally our expert will bring in additional support from DHC colleagues to ensure top-tier coverage of multifaceted client needs.

Four examples of common reasons clients may be in need of interim leadership support are as follows:

a. **Staffing vacancies.** Occasionally organizations find themselves needing interim support to keep operations running while they hire a role internally, whether during the initial staffing ramp up for a young company, during an extended employee leave, or as a replacement for an employee who left the organization. With years of experience in leading departments, DHC SMEs get up to speed quickly, hit the ground running, and step in to seamlessly drive timelines to meet the company's needs.

b. **During acquisitions or mergers,** it's common for one or more site to be brought under the umbrella of their new parent company: in those instances, our experts can act as a Site Manager, COO, or CTO to ensure momentum is maintained during the transition, while allowing time for the company to find the right permanent leader for the position. Alternatively, some companies reconsider staffing levels due to growth, technical changes or improvements, site redesign, etc., and need a consultant who can reallocate resources effectively while protecting timelines.

c. **In the event of a downsizing,** DHC experts can step in to lend a hand in stabilizing operations while the company works to reposition itself for a more optimal future state.

d. **Bringing top-tier expertise to particularly challenging situations.** Sometimes, a challenge emerges that is beyond the experience of current staff. Solving these issues may require the support of someone with either different or deeper technical expertise. The breadth and depth of DHC's experience in working with 200+ clients a year enables us to bring unrivaled expertise to address even the most complex development challenges faced by our clients.

The Impact

DHC's goal is to progress the field of CGT by helping organizations get to their next step(s) in a timely and effective manner while planning for future growth. In any of these situations, DHC keeps each client's product or process on track and moving forward for as long as the client requires support (engagements have ranged from a few weeks to several years). We step back and hand operations off to the client once they find themselves in a self-sufficient position. Embedding our experts can be extraordinarily helpful in minimizing disruption during change but these needs rarely, if ever, require a permanent DHC-based solution. Our emphasis is always on helping each client operate as efficiently, effectively, and independently as possible.

Transforming an Academic Nonclinical Data Package for IND Readiness

Why DHC?

- Expand Client Bandwidth
- Provide Additional Technical Expertise
- Solve Existing Problem (Remediate)

The Ask

The discovery of cutting-edge cell and gene therapy modalities often stems from innovative academic centers, who may then seek to partner with a biotech organization to engage in formal product development and to advance these promising drug candidates to patients. In this instance, a client developing a CAR-T cell therapy licensed from an academic institution hired DHC to provide full support in developing a pre-IND and subsequent IND-enabling nonclinical strategy based predominantly on *in vitro* and *in vivo* studies conducted at the academic center. In addition, and as is typical in these scenarios, the nonclinical studies were performed using drug product generated with an earlier production process that was being developed for GMP-readiness in parallel to the aforementioned regulatory activities. This engagement combined 4 of DHC's Service Domains, namely nonclinical development, regulatory affairs, process development, and analytical development.

Service Domains

DHC's Approach

- The first step was for DHC to evaluate the client's current-state nonclinical package and identify the critical efficacy and safety data to highlight in a pre-IND submission to the FDA.
- Upon agreement with the client on the key nonclinical datasets to include, DHC authored the pre-IND, which enabled the Agency to provide meaningful feedback on the potential acceptability of the nonclinical package for IND. This also informed the messaging that would be required to support the nonclinical package for the IND.
- In collaboration with the client, DHC utilized deep in-house expertise to reframe the academic datasets to author detailed nonclinical study reports and nonclinical summaries for the IND, whilst simultaneously ensuring clear and consistent messaging throughout the submission to ease review. This included a focus on the program's robust and diverse *in vitro* and *in vivo* efficacy data generated at the academic center, whilst leveraging outsourced *in vitro* studies to further bolster the *in vivo* safety findings.
- Furthermore, DHC and the client collaborated to provide concise argumentation on the suitability of: (i) the presented nonclinical datasets, (ii) the drug product material used for these, and (iii) the associated drug product analytical testing strategy, to support the progression of the CAR-T cell drug product to first-in-human testing. Additionally, DHC leveraged available nonclinical literature from similar CAR-T cell programs already in clinical testing to further support the client's nonclinical position.

The Impact

By working with Dark Horse, the client submitted a well-crafted pre-IND package, which enabled actionable Agency feedback and a clear roadmap to IND submission. Subsequently, DHC and the client worked in collaboration to craft a robust and detailed nonclinical narrative for the IND, which resulted in its clearance with no hold comments or information requests from the Agency.

Clinical Regulatory Writing and Focusing Regulatory Strategy

Why DHC?

- Expand Client Bandwidth
- Provide Additional Technical Expertise
- Solve Existing Problem (Remediate)

The Ask

Sometimes a client comes to DHC with a request that shifts dramatically upon our experts' evaluation of available documents and gathering of additional information. In this instance, a small-to-midsize company with an understanding of clinical needs (but with limited regulatory experience) initially came to DHC for document review and help with providing a list of pre-IND questions. Their goals included an expansive vision for their product development and an urgency to get a pre-IND meeting accepted within 30 days of project initiation for investor/fundraising purposes. In addition to the time constraints, the original goal was ambitious because the product is intended to be used in combination with various other products and could also be used to treat patients across multiple disease indications. The client was originally planning to send a package proposing this full range of treatment options to FDA.

Prior to engaging with DHC, another consultancy had begun this work for the client. The client came to DHC because they were experiencing concerns about timelines and the lack of attention that they felt that their project was receiving. Upon receipt, DHC recognized that the package as prepared by the other consulting practice was inadequate for submission to FDA and that the regulatory advice was inappropriate for the development pathway. Specifically, the previous consultants didn't recognize that the original proposed clinical development plan was not feasible due to detailed regulatory constraints. DHC consultants identified the regulatory challenges: a meeting package with this wide of a developmental scope would make it through regulatory review in the time available, and likely would not be possible without a step-wise development plan. DHC therefore helped the client narrow the focus of their initial product development to ensure that they would reach the clinic as quickly and efficiently as possible. This more expedient development pathway still allowed for their future goals to be realized…it just used a more step-wise approach.

Service Domains

DHC's Approach

The first need was to clarify the client's ultimate goals for the product and then identify a way—by narrowing the scope—that they could get regulatory feedback in short order so as to get their product to the clinic quickly, which was also a goal of their investor. DHC worked with the client to revise the clinical development plan, simplify the trial design and patient population, and help author both the meeting package and the clinical trial synopsis. Authoring the clinical section of a pre-IND requires a deep understanding of patient populations, disease indications, manufacturing processes, regulatory expectations, and the inherent limitations of all of the above. DHC brought a team of relevant subject matter experts to the project to ensure that all of these considerations were addressed.

The client's previous engagement with another consultancy had gone poorly, without the client receiving either sufficient attention or adequate advice. In contrast, DHC was able to step in quickly and meet the challenging timeline due to our unique combination of nimbleness and depth and breadth of CGT knowledge.

Once DHC took over the protocol synopsis and focused on linking product end goals to clinical development, the preparation of the pre-IND meeting request and briefing package went swiftly. Additionally, our writers prepared pre-IND questions intended to maximize probability of success in obtaining clear FDA feedback.

The Impact

The client achieved their first business goal: a timely and concise FDA submission. Successful completion of the meeting provided the client with responses clarifying FDA's expectations for launching the first clinical trial. The client also now has a detailed understanding of how to segment their goals in order to maximize each opportunity before moving on to the next. Focusing a first step of development is necessary for even those most expansive long-term visions.

Interim CMC Lead Helps Address an LNP-Based Drug Product Shortage

Why DHC?

- Expand Client Bandwidth
- Provide Additional Technical Expertise
- Solve Existing Problem (Remediate)

The Ask

This client was experiencing a critical shortage of drug product to supply ongoing clinical trials and were about to run out of clinical material. The client had recently changed the CDMO that was manufacturing the LNP component of their drug product (DP), while additionally modifying its manufacturing process so that a tech transfer was not feasible. Additionally, drug product stability issues were being investigated. Relationships with multiple drug substance (DS), critical component, and DP manufacturers were broken, and several lots of DP had failed to meet acceptance criteria and were therefore unusable. The loss of these DP lots compounded the already tense relationship between leadership and the CMC/MSAT groups and brought the client perilously close to reaching the end of product shelf life and product availability for the current inventory. With only a few months of clinical supply remaining, and a 3-4 month manufacturing process timeline, the client reached out to DHC for help with CMC issues, repair of their CDMO relationships, and ultimately clinical resupply.

Service Domains

DHC's Approach

DHC provided interim leadership, overseeing CMC, clinical manufacturing, and CDMO activities throughout resolution of the crisis. This allowed the client to fill critical personnel gaps while DHC remediated the problems.

Bringing in CMC leadership, technical expertise, and project management SMEs, DHC led the implementation of an improved and scaled-up LNP process at the new CDMO, addressed stability issues, and put plans in place to better monitor drug supply chain. DHC also began the delicate work of repairing relationships with the CDMOs through leadership changes, technical expertise, and by implementing PM best practices.

One of the largest challenges was a change to the LNP manufacturer along with the implementation of new and scaled-up process. The scale-up involved the implementation of a new, industrial-scale piece of equipment. As a technical transfer was not feasible due to the process changes, the DHC team established strategies for qualifying the process as suitable for clinical drug product manufacturing.

Scale-up of the process yielded a number of additional questions (e.g., what is the potential impact on the polydispersity? how has the diameter of the LNP changed?, etc.), all of which culminated in the need to identify the potential impact of these changes to the DP, and to identify the appropriate CQAs for the LNP, DS, and DP.

To further complicate the issue, LNP-based drug products have a unique set of analytical considerations which need to be addressed for characterization and release testing. A common problem is utilizing a test method that doesn't sufficiently characterize the drug product based on related regulatory guidance. In this instance, DHC worked alongside the client's analytical leadership to establish appropriate analytical testing panels to support both early-stage and late-stage trials. Leveraging an evolving DP analytical testing strategy early on, and bolstering that strategy throughout clinical trials, provided data to support late phase comparability, bridging, and validation activities.

The scope of DHC responsibilities and involvement with the client has continued to expand and now includes managing production forecasting, oversight of all CMC mfg activities, strategic planning, and authorship/revision of regulatory documents.

The Impact

DHC sped up and improved the client's manufacturing process, generating material suitable for drug product manufacture to successfully release clinical GMP drug product with little to no impact on the clinical supply. This allowed continuation for current patients as well as the enrollment of additional subjects. DHC also established a manufacturing forecast to ensure that future clinical supply would be met. DHC identified, prioritized, and implemented further manufacturing improvements and analytical strategy for support as the client transitions to later stage clinical trials.

A Roadmap to IND

Why DHC?

- Expand Client Bandwidth
- **Provide Additional Technical Expertise**
- Solve Existing Problem (Remediate)

The Ask

For a roadmap to IND the most commonly asked questions are: how much time will it take us to get to IND, how much will it cost, and what are the key milestones? These requests typically arise from early preclinical stage programs just beginning their transition from discovery to formal product development. Often clients will have demonstrated *in vitro* proof-of-concept and completed one or more pilot animal studies. The client may also have high level CMC development and nonclinical study plans for which they are seeking DHC review and input. In other cases, clients come to DHC during mid- to late-stage preclinical development, wanting to ensure that their nonclinical IND-enabling study plan is appropriately aligned with CMC activities. Having a clear, integrated, cross-functional project plan that includes timelines, costs, and value inflection milestones is also a critical success factor for fundraising.

Service Domains

DHC's Approach

An effective roadmap to IND considers both efficacy and safety through the lens of the client's business strategy and risk tolerance. It addresses timeline and budget, including an in-depth expectation of what the client's future capital needs will be over time. Typically, a deliverable will include a Gantt chart to provide side-by side tracking of various nonclinical, clinical, regulatory, and CMC activities to ensure that these are synched up appropriately in a way that will translate into an achievable timeline. Tying costs into this chart is also necessary for identifying where in the process the client might need a cash infusion.

Capturing regulatory interactions is critical: when should a pre-IND meeting be planned in the schedule? Would the product be appropriate for and benefit from an INTERACT meeting or from another early engagement forum such as CBER Advanced Technologies Team (CATT)? The roadmap will include where those interactions make sense in terms of the overall project architecture and what data sets should be viewed as 'must haves' versus 'nice to haves' to enable a successful regulatory engagement.

DHC consultants build an understanding of the intended clinical use of the product and the proposed efficacy models and then collaborate and consult with the client to understand the overall development trajectory as well as key driving factors such as what the study needs are in order to determine a starting clinical dose. Depending upon the complexity of the model and the dose administration procedure, DHC will discuss and advise on appropriate study plans to support the intended use. DHC can provide advice on guiding delivery methodology: whether an off-the-shelf option is available or if a custom device is needed (and if so, what the development path for that device may look like).

Some clients already have draft nonclinical study designs to consider and some need assistance in putting them together. DHC consultants take into account suitable study size, what the endpoints are, how many studies are needed, how to determine dose-ranging, selecting a suitable CRO, and so on.

Upon client request, DHC consultants offer a draft study plan complete with current pricing information from one or more CDMOs/CROs. Vetting and selection recommendations for choosing a manufacturing partner may be another DHC project.

Sometimes the IND roadmap is supported by a hiring plan, should the company be in growth mode. DHC's industry experience allows for a keen eye on what expertise will be needed at what point in time and how and when to allocate a full-time employee in-house vs. when to contract out support.

On occasion DHC receives an accompanying request to build a pitch deck for a round of fundraising. Investor interest can be dependent on receiving the details laid out in a roadmap, because knowing each step of the process not only increases investor confidence but helps to define use of proceeds and identify the critical value inflection points that will enable each future round of fundraising.

The Impact

A DHC-provided roadmap to IND ensures a robust review and deep technical (and industry-specific) understanding of a program's current standing, with a clear set of recommendations of next steps. Some clients begin pursuing those next steps immediately, while others use the roadmap to enter a fundraising round first. A detailed roadmap demonstrates to investors a cohesive plan for use of proceeds, including activities, costs, timelines, and inflection points.

Due Diligence for Cell Therapy Company Formation

Why DHC?

- Expand Client Bandwidth
- **Provide Additional Technical Expertise**
- Solve Existing Problem (Remediate)

The Ask

A prospective investor client approached DHC with a fast-turnaround request for an assessment of a business proposition: merging two cutting-edge CGT technologies to spin out a new cell therapy company. One asset had promising early clinical safety and efficacy signals for its early clinical stage cell therapy products. The second target asset had a state-of-the-art technology to enable a next-generation approach to those products. The ultimate goal was to combine these two technology platforms to be able to build out new therapeutic pipeline products. DHC needed to consider both of these assets from the perspective of CMC, nonclinical and business risk, evaluate terms of manufacturing agreements, and consider the scientific rationale for merging these two platform technologies. Additionally, DHC advised the client on the intended budgets, hiring plans, timelines, and milestones for the new entity.

Service Domains

DHC's Approach

As with most due diligence projects, the timeline of this request was accelerated to align with the predetermined deadline for either agreeing to the deal or walking away.

A key element of the request was to evaluate business risk: specifically, the overall cost projections for continued future development of each asset. The client had prepared a draft financial business plan that DHC was to review to ensure alignment with industry standards. A first step was to consider whether the costing proposal was sensible: did the numbers represent realistic cost expectations?

DHC performed a deep dive review of data rooms supplied by both target assets, allowing for a detailed look at the CMC and nonclinical current state and future development plans. This review included nonclinical data packages that had been previously generated in addition to budget, timelines, and past regulatory correspondence (for both US and non-US health authorities). DHC summarized the merits of the investment, identified potential development risks, and aligned on appropriate strategies and proposed partnership opportunities.

On-site diligence included DHC travel to current sites for both assets, as well as to the intended manufacturing partner for the new company. This enabled a technical and quality review of all facilities and ongoing operations in addition to an in-depth business strategy discussion with leadership for both target assets. Leadership for all parties involved attended this onsite quality and technical review, which allowed for strategy partnership and business discussions between investors and both target assets with DHC present. This offered a high degree of transparency for all parties.

This client ask evolved over time, with DHC eventually becoming responsible also for evaluating and providing input on the documents for the agreement itself. Although Dark Horse Consulting does not provide legal advice, we reviewed and evaluated the master service agreements and key elements of the deal from a quality, technical, and business perspective in partnership with the client's legal advisors.

In the final stages of the discussion, DHC met daily with the client and their lawyers to assist in finalizing documents to broker the deal, ensuring that they could meet their deadline.

The Impact

The client considered both assets sufficiently de-risked to warrant finalizing the purchase, especially considering the adjustments DHC recommended making to the deal.

Dark Horse also provided the client with sufficient confidence regarding assurances of what quality, CMC, and regulatory needs the program would likely require and how long they were expected to take. Another outcome of this diligence experience was that the investor now has a better understanding of what will go into completion of a successful licensure, providing more control over the future of the asset.

CGT Manufacturing "Hotel" Facility

Why DHC?

- Expand Client Bandwidth
- **Provide Additional Technical Expertise**
- Solve Existing Problem (Remediate)

The Ask

A U.S.-based company planning to develop and build a multi-tenant "hotel"-style facility for early-stage CGT manufacturing required strategic guidance. This included a review of the facility conceptual design with voice of customer interviews, facility demand modeling, and the development of market insights, all to inform the client's planning and decision-making process.

Service Domains

DHC's Approach

Engaging Dark Horse at an early stage of business case development provided the greatest opportunities to influence the strategic direction of a project. In this project, the client planned a new GMP facility providing leasable suite space to multiple tenants, with DHC providing recommendations for key issues such as:

- Operating cost and pricing models
- Facility design and suite layout to maximize flexibility to accommodate multiple CGT modalities
- Regulatory considerations for multi-tenant occupancy of a "hotel"-style GMP operation
- Facility demand forecasting and targeting of potential tenants including region-specific analysis
- Benefits of a hotel facility over conventional build-or-buy manufacturing scenarios
- Positioning of a hotel service offering and competitive landscape analysis

Within each suite, the DHC team defined the CGT modalities, scales, and equipment types that would be best suited to the proposed clean room layouts. The DHC team also developed details of tenant services that should be provided by the facility landlord and recommendations for how to ensure flexibility for the diverse range of customers needing to be accommodated.

Revenue modeling and pricing benchmarks for tenant services were also provided to the client for use in building out their detailed financial models. Demand modeling was provided to forecast 10-year growth in the need for CGT manufacturing space, broken down by modality.

Finally, DHC made initial recommendations for positioning the client's proposed "hotel" facility within the spectrum of currently available service offerings, illustrating the competitive landscape with case study examples.

Throughout this project, DHC ensured that a broad team of consultants provided their expertise to cover facility design, business strategy, regulatory compliance, and market analysis skill sets.

The Impact

DHC's facility design review provided a valuable set of recommendations that were used by the client's architect to improve and refine operability, flexibility, and compliance of the facility. This included a careful focus on shared areas of the building and controls needed to segregate tenant operations and manage GMP flows of people and materials. DHC's work allowed the client to refine their planned hotel facility service offering with a focused set of facility user requirements, target customers, market positioning, and critical revenue/cost data.

Cell Therapy Facility Retrofit

Why DHC?

- Expand Client Bandwidth
- **Provide Additional Technical Expertise**
- Solve Existing Problem (Remediate)

The Ask

A U.S.-based academic organization engaged DHC to provide an independent design and regulatory review of plans for a retrofit of an existing building to serve as a facility for early-stage manufacturing of HCT/Ps and cell therapies. This included an initial assessment of the available capacity of the facility to ensure that customer requirements could be met.

Service Domains

DHC's Approach

DHC utilized its collective experience in performing facility design reviews for clients across multiple greenfield and brownfield projects in supporting this client request. Academic facilities require flexibility for multi-product manufacturing, and the team incorporated key requirements to ensure that the facility design was safe, efficient, flexible, and compliant, allowing it to support the needs of the academic organization in question while still having the capability to meet the stringency of GMP requirements in a stage-appropriate way.

In this case, an existing building was to be retrofitted as a cell therapy facility, including ISO7 and ISO8 clean rooms. Known constraints included:

- Limited building footprint
- Restricted headroom in which to accommodate complex HVAC ductwork, mechanical systems, and building controls
- Limits on allowable roof loadings for new air handling units
- Insufficient provision of utilities, particularly electrical power, for a more energy-intensive new application

An independent design review is an excellent way to pressure-test a facility concept design. For this project, DHC drew from the design and operational experience of team members who have worked in academic and commercial CGT facilities. DHC was able to provide specific feedback on a variety of issues, including:

- Clean room sizing, quantities, and classifications required to meet the needs of the product portfolio.
- Optimization of clean room operation through production segregation, equipment selection, and placement.
- Adequacy of supporting spaces, such as materials storage, laboratories, and changing rooms, to serve the core GMP production areas
- Management of HCT/Ps and regulatory considerations for those vs. more complex biologic cell therapy products (Addressing both of these needs required manufacturing segregation to optimize production.)
- Improvement of flows to ensure GMP compliance and increase production efficiency
- Specifying air handling system zoning and pressure regimes to assure adequate segregation between different products
- Building infrastructure condition and required modifications
- Project execution strategy, assessment of clean room contractors, and extent of modular construction techniques

The Impact

DHC's design and regulatory review allowed the client to validate their current concept study facility layout, assess the expected manufacturing capacity for different products in their portfolio, and make focused changes based on DHC's recommendation to enhance the design and help drive the project forward.

As a result, the client could be confident in their approach to redeveloping their available building in an optimized way to address the diverse needs of the product portfolio it was intended to serve.

The Value of DHC's Project Management Toolbox

Why DHC?

- Expand Client Bandwidth
- Provide Additional Technical Expertise
- Solve Existing Problem (Remediate)

The Ask

The initial project request for this client wasn't specifically for project management—it was instead for remediation, to address and identify a suitable validated/compendial analytical method for final product testing. The client's request to DHC included managing the third-party vendor: the lab that was executing this work on behalf of the client. DHC discovered that overall cohesiveness and communication between the CRO and client was impeding project momentum, and recommended streamlining communication and formalizing the reporting mechanism between the two groups to strengthen collaboration and speed up the process. The client opted to add DHC's project management services to ensure an industry-savvy point person who could provide overall project goverance.

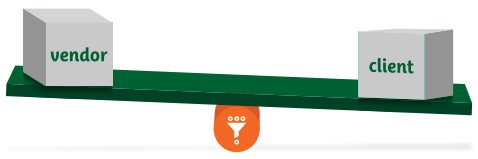
Service Domains

DHC's Approach

- Once the DHC PM had been identified and introduced themselves to the client-side contact and the vendor-side contact, it was time to set expectations. Consistency and accountability are two of the reasons a single point of project management contact is useful, and if that individual isn't affiliated with either of the two original parties, then they also bring with them an often-needed sense of neutrality.
- A PM can be necessary to track the moving pieces in a multi-part project...or to add urgency to drive a project forward...or both. In this case, the client needed a driver to act as an extension of the client: someone to keep the pressure on to ensure that the project would build sustainable momentum to achieve the desired timeline.
- The project manager introduced the items from within the P&PM "toolbox" that they recommended for use for this project. The typical toolbox set may include agenda templates, planning documents/templates, risk registers, a project charter, timeline, meeting minutes, meeting agendas, supply chain and/or lot tracking, and/or a project dashboard.
- Communications expectations were set, including how and when to provide updates, tracking, and any other reports to the client.
- DHC's PM selected software tools that were an appropriate match to the office software preferred by both the client and the vendor.
- Whenever any element of the project was delayed, jeopardized the overall therapy timeline, or was otherwise problematic, the DHC PM escalated the issue through the vendor, to ensure that the final products remained on schedule and at the highest level of performance.
- The DHC PM was responsible for the overall project governance, taking ownership to ensure that deliverables remained on schedule.

The Impact

The client received the benefit of a steady voice keeping continuous (and tracked) lines of communication open between the client and their contract lab, providing timeline tracking and visibility into the status of the project. The project achieved its goal timeline, which was at risk at the time when the DHC PM entered the picture. The relationship between the client and the vendor was significantly strengthened.



DHC's expert Project Managers can act as a fulcrum, connecting and balancing the relationship between clients and third-party vendors.

Pegasi: COGs and Facility Planning

PEGASi

Why DHC?

- Expand Client Bandwidth
- Provide Additional Technical Expertise
- Solve Existing Problem (Remediate)

The Ask

An international tools and technology company requested a market analysis of the gene-editing and advanced therapies space as well as a facility buildout plan to manufacture a critical component for gene therapy applications.

Service Domains

DHC's Approach

Providing realistic future expectations for the client required an understanding of the many elements at play. DHCs internal experts provided assistance in identifying components that would be involved in the client's strategy and how they would interact with one another, from market size to facility requirements to regulatory and beyond.

This request also made use of DHC's proprietary data-modeling platform: Pegasi. This platform is flexible, applying customized input to quantitatively describe a range of probable outcomes for a variety of client queries. In this case study, DHC's Quantitative Modeling team focused on use of the market analyses, COGs assessment, and resource modules of the Pegasi platform.

The client had not previously produced this critical manufacturing component, but they did have experience with a related product and had a clear vision of what percentage of the market they would need to capture and within what time frame in order to meet their related revenue projections.

This clarity allowed DHC to work backwards from the market expectations to arrive at expectations for process and facility for producing the requisite amount of raw material.

The first step in this exercise was to estimate the market demand. Dark Horse conducted a landscape scan in addition to VOC surveys for a clear picture of the current market need and also to consider the growth of the market over time. Once the market demand forecast was quantified and target ranges for market penetration over time were applied, the DHC team had a clear view of the production demand the client could expect for the critical component.

With the demand known, the DHC team identified and quantified the process equipment and infrastructure systems necessary to meet the production demands, then produced a sample facility map outlining production suites and supporting space. Included in this facility map were expected schedules for the multi-phase facility buildout, with the facility expansion aligned to the estimated market growth and market penetration.

The DHC team considered how a manufacturing effort of this size would reside within the client's current infrastructure, complete with a review of the full complement of labor (how many individuals with which skill sets would be necessary to begin and continue work on a site of this size) down to hazardous materials usage and waste disposal. After modeling the demand, infrastructure, and labor, DHC was able to analyze not only the COGs and anticipated revenue but also the sensitivity of the profit ranges in response to changes in any variable fluctuation.

Due to the evolving nature of the regulatory framework for CGT in general, and this manufacturing component in particular, it was critical to include a regulatory assessment to complete this exercise. DHC regulatory experts identified regulations currently in place in various markets, provided best practices recommendations, and weighed in on the direction regulatory guidelines may go in the future.

The Impact

Pegasi's results were presented to the client and considered within the clients' portfolio and company mission. First to consider the final materials was the relevant team in charge of implementation, to ensure an internal alignment of expectations. The results also went to senior management to ensure that they had clarity on all decision points for adding this opportunity to their range of business offerings.

Facility Design: Final Design Review

Why DHC?

- Expand Client Bandwidth
- Provide Additional Technical Expertise
- Solve Existing Problem (Remediate)

The Ask

An EU C&GT contract manufacturing organization developing a large-scale multi-modal manufacturing facility needed support with late-stage design reviews. This project was extremely time-sensitive given the degree of work on the project that had already been done before bringing Dark Horse in as a consultant.

Service Domains

DHC's Approach

- The first step in this process may well sound like a final step: the design for the facility was already partially decided when DHC was brought on to do what was expected to be a final review of the planning documents and schematic drawings. An important take-home message from this case study, though, is that it is never too late to get an experienced eye on the facility design. An experienced C&GT engineer can recommend practical design improvements at most stages of development.
- When looking at the full set of engineering diagrams, DHC's consultants discovered that while the clean room suite design was fine from a mechanical engineering viewpoint, there were significant issues with personnel and material flows and the relative sizing of the facility. Additionally, there was insufficient storage and staging space identified in the design.
- DHC continued to review the facility design documents, bringing to light a number of additional design improvements. One particular opportunity of note that was possible at this stage: optimizing flows of material and of waste.
- DHC was able to provide a de-bottlenecking analysis, based on the current facility design documents, to improve the flow of materials and waste through the manufacturing suites and the supporting production areas. DHC knowledge of cell and gene therapy processes was key to developing a series of recommendations to improve production efficiency and also to reduce risks of cross-contamination and mix-ups. Relatively small adjustments to the design delivered significant operational improvements that still benefit the facility today.

The Impact

Dark Horse identified a significant number of operational improvements that proved highly valuable both in timing (the design changes were able to be implemented during the construction of the facility) and in concept (if the design issues that were in place thus far hadn't been remediated, it could have had a negative impact on the facility's long-term operability and regulatory approval).

It is critical to note that when making significant changes like these, the degree of material difference that DHC and clients can achieve together is highly dependent on whether the client is amenable to change and to hearing alternate points of view. In this case, the client's openness to the process made quick pivots possible without delaying the project and heralded a successful launch.

Embedded Early for de novo Support

Why DHC?

- Expand Client Bandwidth
- Provide Additional Technical Expertise
- Solve Existing Problem (Remediate)

The Ask

Many DHC clients request support when they reach a point in development where they have problems or questions that they cannot answer, or need additional bandwidth to continue. Some clients, such as this pure-play gene therapy client, though, request support very early in the process so as to have continual assistance. In this case, DHC was brought in by the lead investor at company formation, just as its programs were being spun out of academia. Funding was already secured and scalability was a known challenge. Academic data was plentiful but, beyond that, the therapy was in nascent stages. Dark Horse worked with this client from the beginning to conceptualize and build a development process that would stand up to the challenges of each future trial phase and into commercial production.

Service Domains

DHC's Approach

Besides the need to translate their research achievements into a commercially viable product, the client's manufacturing process would have sufficed for Phase 1…but wasn't scalable (or at an appropriate quality level) beyond that. DHC provided support for all elements of CMC: building a manufacturing process that would prove strong enough to translate into industrialization.

Preclinical proof-of-concept studies by the academic partner included two transgenes and two plasmid systems. DHC consultants re-sequenced the plasmids, transferred to a three-plasmid system to align with current best practices for regulatory compliant AAV production, and led the vendor selection process for plasmid synthesis, cell banking, and production.

After redesigning and manufacturing the plasmids, Dark Horse went through an RFP process to identify a contract manufacturing partner for the vector that would meet the long-term needs of the developer. Particular consideration was given to use of GMP-grade raw materials and a scalable manufacturing platform to limit the degree of comparability testing that would be necessary as development progressed.

Many pieces of the process were happening in parallel, such as working to get sufficient research grade plasmid, while simultaneously beginning the manufacturing of a GMP-grade plasmid to be used later in development. Regulatory needs were also a consideration in this project. DHC experts wrote the CMC section for the pre-IND and participated in accompanying regulatory discussions.

On the process development side, identifying and testing cell lines was top of mind, as was the need for process parameter optimization and demonstration of scalability. The DHC-chosen manufacturer made materials to support preclinical studies at the same time as working through the process development.

Documentation is critical at each stage, particularly when proceeding from development to manufacturing. Dark Horse took point on every GMP document, every batch record, and every analytical qualification, representing the Quality function for the client in review and approval of all manufacturing and test method qualification documents.

Any remediation needs were addressed via technical troubleshooting during development.

The Impact

Having a DHC team continually engaged as the technical operations lead allowed for support of everything downstream of research: from process development to CMC and regulatory support to manufacturing support, etc. Dark Horse provided certainty that each step was being done to the highest levels of technical proficiency along with the long-range consideration, planning, and analytical awareness that characterize successful therapies. Dark Horse cannot, of course, guarantee the success of any therapy, but our teams can guarantee an optimized process and a 360° technical and strategic viewpoint to give therapies the best possible chance at successful commercialization.

Remediation of CRL Issues: Prep for BLA Resubmission

Why DHC?

- Expand Client Bandwidth
- Provide Additional Technical Expertise
- Solve Existing Problem (Remediate)

The Ask

This client had late-stage experience….but not with cell or gene therapies. In a younger industry such as C&GT, previous agency guidance is not yet as robust as it is for fields that have been around longer. For that reason, sponsors benefit from C&GT-specific expertise. The client came to Dark Horse to request remediation and resolution of multiple areas for which their original submission was rejected. Due to the time constraints of resubmission, a sense of urgency accompanied getting the product back on track and executing each element of this process on time and with quality as a top priority.

Service Domains

DHC's Approach

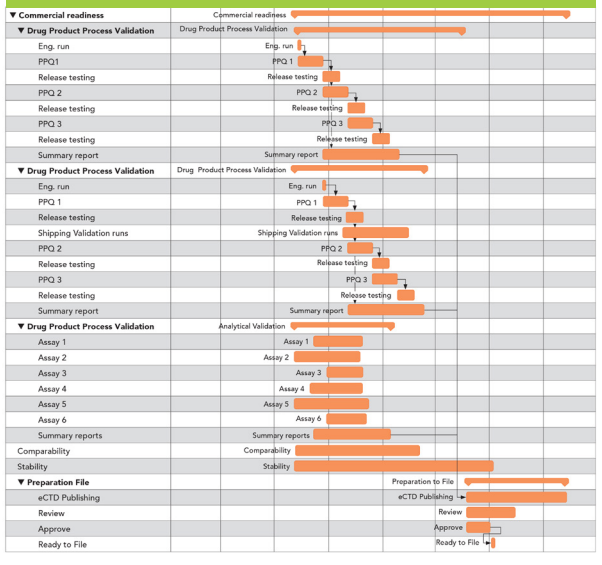
This engagement addressed a wide range of overlapping service areas spanning at least six of DHC's twelve Service Domains. Among the many services provided by DHC were:

1. Strategic regulatory support to identify the path to issue resolution and BLA resubmission
2. Tactical/operational regulatory support such as document authorship of briefing book and BLA subsections
3. Creation of a cross-functional project plan detailing the range of necessary activities and sequencing; accompanying detailed project Gantt charts and dashboards for visibility and tracking completion as well as critical path mapping
4. Technical expertise relating to C&GT analytical, process development and manufacturing, to ensure technically sound remediation to quality and regulatory concerns in these areas
5. Management and oversight of relationship with an external testing house requiring special attention for deliverables on and near the critical path for resubmission
6. Root cause analysis of process failures to accelerate issue identification and remediation

The Impact

The client successfully completed their post-rejectio regulatory agency meeting, allowing for next steps towards resubmission. Dark Horse's C&GT-specific project management plan provided necessary clarity and visibility for efficient and effective project remediation along with critical path mapping. Additionally, DHC's subject matter expertise and technica know-how, combined with project leadership skills, not only prepared the client for their resubmission (along with potential submissions in different regulatory jurisdictions), but also set them up for future successes.

Major Activities for BLA Resubmission



Quantitative Modeling May Yield the Unexpected

Why DHC?

- Expand Client Bandwidth
- Provide Additional Technical Expertise
- Solve Existing Problem (Remediate)

The Ask

It's common to consider a detailed review as a way to capture problem areas. Sometimes, though, a review can bring to light how little actually needs to be changed. In this example, a client who was beginning enrollment for a clinical trial decided to request a quantitative review with a specific manufacturing focus to help isolate any unforeseen future issues. The answer surprised them.

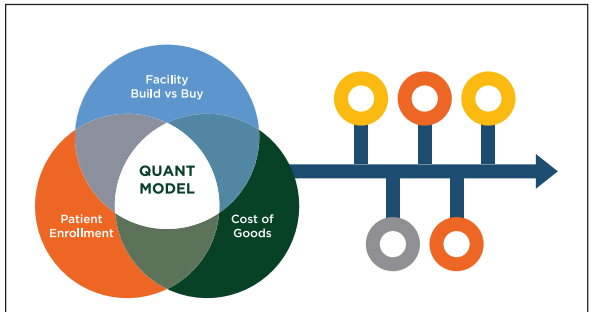
Service Domains

DHC's Approach

- This client's preliminary internal review indicated a range of likely limitations that needed confirmation, including the possible need for more manufacturing capacity.
- As is our standard, we required a detailed questionnaire specific to our queries to help isolate input assumptions: materials costs, process duration and yield, clinical enrollment, and probabilities of success. DHC, as always, was able to offer any necessary level of guidance in completing this assessment based on process specifics and industry standards.
- The Dark Horse process is able to not only consider the overlap in manufacturing capacity (build vs. buy), COGs, and patient enrollment, but to follow that overlap through the dimension of time. Whether the timeframe in question is a broad or narrow range depends on the client's current stage and future needs, so the initial questionnaire also requests timeframe ranges for each phase of development.
- After assisting the client in completing the DHC questionnaire, it became clear that the client did not have the set of problems that they expected. DHC's expert consultant therefore adapted the expectations of the "ask." Instead of using our proprietary software (which would have been unnecessarily complex for this situation), she provided a truncated and customized model that was specific to client needs and based on their precise situation.
- Considering the reality of the limitations that existed (rather than perceived or anticipated limitations) made it possible to focus more efficiently on the few necessary solutions, and to plan for immediate and future clinical stages.

The Impact

Within a very short timeframe, the client received the answers to their questions and discovered a much quicker and easier fix than they had expected. In this case, the model demonstrated that there were significantly fewer changes required to their existing manufacturing strategy than were expected. The client was able to proceed with the trial with peace of mind knowing that not only were they prepared for this stage of clinical trials, but for future stages as well.



Our quantitative model takes time into consideration as another dimension.

Comparability Review in Preparation for BLA Filing

Why DHC?

- Expand Client Bandwidth
- Provide Additional Technical Expertise
- Solve Existing Problem (Remediate)

The Ask

The burden of proof of comparability rises sharply by the time therapies arrive at Pivotal/Phase III, especially given the likelihood of manufacturing process changes before arrival at that stage. Add that to the recent string of BLA rejections and late-stage product delays relating to analytical characterization of CGT products, and any biotech would be wise to proceed with caution. This client, advancing through their cell therapy product's late-stage development review for use in fighting a non-orphan disease, enlisted Dark Horse as a second set of expert eyes. DHC's role was to provide an independent review of their comparability package, complete with a comprehensive gap analysis and risk assessment, in preparation for their upcoming Biologics License Application (BLA filing).

Service Domains

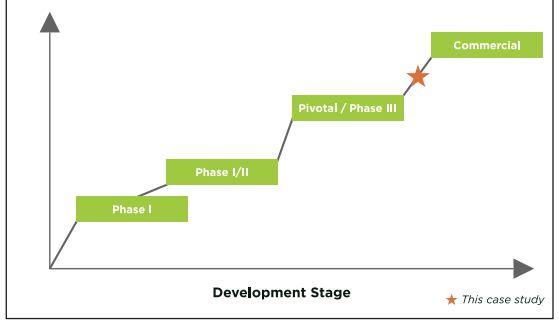
DHC's Approach

- A late-stage project brings with it a significant amount of material (historic data files, documents, agency correspondence, presentations, etc.). The first step was to do an extensive review of the entire history of the Phase I and II clinical trials in addition to a review of prior dialogue with the regulatory agency. This review effectively considered past responses to agency questions or concerns and provided a road map ahead for future expectations and questions.
- In addition to clinical data for safety and efficacy, extensive process data was also necessary for review: manufacturing processes (including changes where relevant) and previous comparability packages.
- Because this project occurred during analysis of the Pivotal/Phase III trial results, additional documents and data continued to come through to the Dark Horse team in real-time as they were generated.
- Dark Horse worked quickly to ensure that the client's internal deadlines remained intact.
- Interim meetings kept the client up to date as the review progressed, providing preliminary feedback and document review questions as well as getting on-the-ground updates as the clinical data analysis continued.
- Once the reviews were complete, the Dark Horse team put together a gap analysis and trademark matrix-based risk assessment of their comparability package and shared those findings with the client along with risk ratings and (where necessary) mitigation recommendations in order to prepare the client to the fullest possible degree for their upcoming interactions with the regulatory agency.

The Impact

The comparability package for this client's late-stage cell therapy, which is a therapy with a potentially wide-reaching impact, was thoroughly vetted and ready to be submitted as part of their BLA filing.

As a therapy proceeds through Phase I / II and into Pivotal—or Phase III—clinical trials, the comparibility burden increases.



Retrospective Failure Analysis and Remediation

Why DHC?

- Expand Client Bandwidth
- Provide Additional Technical Expertise
- Solve Existing Problem (Remediate)

The Ask

Sometimes during an analysis of data, manufacturers will identify nonsensical or counterintuitive results. Recognizing that the data is somehow "off" is a first step. A second step is to call in someone like Dark Horse with remediation experience to investigate and ask the necessary questions, with a goal of identifying the source(s) of the issue. This client, an established biotech, was facing problematic data from performance of a new assay at its CDMO and needed assistance in tracking the problem(s) back to the source.

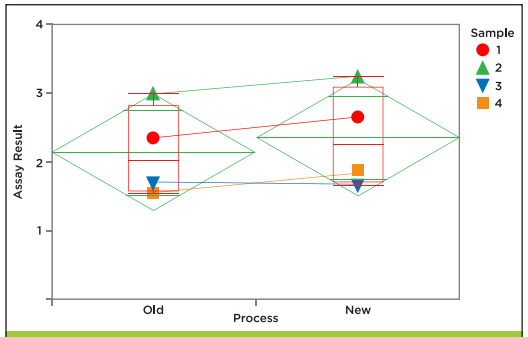
Service Domains

DHC's Approach

- In this case, the client was implementing a new assay format at its CDMO in response to an FDA request for increased characterization of product potency as part of a comparability study.
- The CDMO was unfamiliar with the assay format in question, and initial attempts to run the assay generated nonsensical data.
- As an initial step, DHC requested and analyzed the raw data in order to generate hypotheses about the likely failure mode(s) at play.
- Next, DHC designed an experiment to test the generated hypothesis regarding likely failure mode.
- A DHC Consultant was on site as a 'Person in Plant' during the experiment to observe CDMO staff performing the assay and to ensure successful execution of the experimental plan.
- Data analysis was performed in real time to enable timely and meaningful feedback during study execution, maximizing the opportunity to identify a definitive root cause without need for further experimentation.
- Following successful remediation of the immediate issue, DHC equipped the CDMO with a training guide describing data analysis procedures, as well as common failure modes and what to look for, to enable greater self-sufficiency in future.

The Impact

The client's project was back on track and the CDMO was able to generate the additional comparability data, as requested by the FDA. Additionally, the manufacturer now had a greater in-depth understanding of the assay methodology and the client had an increased sense of confidence in their manufacturing partner. The CDMO was also now prepared to be able to explain the "why" the next time an assay yielded unexpected or undesired data.



Once the assay was remediated, the client was able to genereate data at the CDMO supporting comparability of the new process to that of the old process.

Convening a Medical Advisory Board

Why DHC?

- Expand Client Bandwidth
- Provide Additional Technical Expertise
- Solve Existing Problem (Remediate)

The Ask

A therapeutic development company sought investment to enable further clinical development of a mid-stage candidate cell therapy, including funding for a licensure-enabling trial. In combination with the findings and recommendations identified and developed through DHC's due diligence of the therapeutic candidate's Chemistry, Manufacturing and Controls (CMC) and Regulatory position, the practice was appointed to recruit, convene and chair a Clinical Advisory Board to provide independent evaluation of existing clinical data to enable an informed view to be developed regarding the readiness and near-term potential for evaluation within a licensure-enabling trial.

Service Domains

DHC's Approach

- The practice appreciates the complexities and sensitivities inherent to the relationship between a Clinical Advisory Board and a therapeutic development organization, particularly in the context of due diligence. It is critical to assemble an Ad Board capable of dispassionately assessing and opining on the clinical and commercial potential of a therapeutic asset, while remaining empowered to identify and highlight strengths, weaknesses, opportunities, and threats, in order to optimize the likelihood of Clinical, Technical, Regulatory, and Commercial success.
- DHC identified and prescreened a selection of top-tier potential Clinical KOLs based on project requirements. In doing this, the client benefited from leveraging and gaining immediate access to DHC's network of top-tier resources.
- DHC analyzed and disseminated data for pre-read and initially conducted individual interviews and group sessions with Ad Board members to evaluate Clinical safety and efficacy data generated during the Phase II trial relative to the company's selected endpoints. The strategies employed to facilitate evaluation of the data enabled KOL opinions to be both gathered on an individual basis and considered in a group setting, including critical consideration of the employed clinical end points relative to the disparities associated with those expected and considered most relevant by different Competent Authorities. DHC's deep expertise in the strategic planning and execution of these evaluations enabled generation of dispassionate, informed positions and clear recommendations.
- DHC assimilated the outcomes of the Clinical workstream together with key findings of the CMC-Regulatory workstream, to generate a comprehensive data package and key recommendations enabling our client to make an informed decision with actionable recommendations proposed where any strategic element was deemed insufficient or suboptimal.

The Impact

DHC's leadership and expertise in executing a first rate Clinical Advisory Board afforded our client an unparalleled opportunity to optimally inform their investment decision, appropriately based on the development of an impartial, multi-factorial evidence-based position.

Market Research For a Cell Therapy Technology

Why DHC?

- Expand Client Bandwidth
- Provide Additional Technical Expertise
- Solve Existing Problem (Remediate)

The Ask

Entering the Cell & Gene Therapy space is an attractive proposition for many companies with diverse product portfolios. Successful entry into such a complicated space, though, requires thorough market research and/or modeling. In this case a full Market Research review, including a Voice of Customer survey, would lead to a forecast revenue model for effective planning.

Service Domain

DHC's Approach

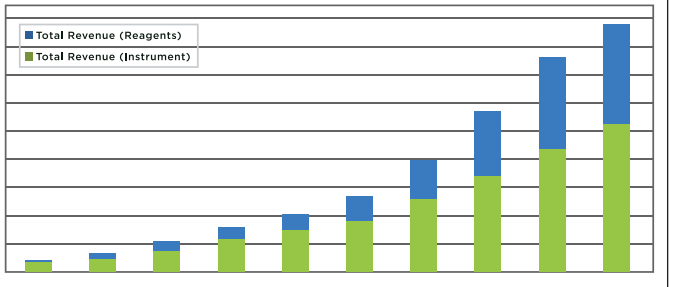
Before releasing a supporting technology into the cell therapy field, this client retained Dark Horse for a full market research workup, including:

- A Voice of Customer survey.
- A portfolio expansion project. Evaluating other technologies in the cell therapy field provided the client with a sense of what they might choose to add to their portfolio. The first step is to consider a landscape scan to identify the other players in the field and their current and future offerings. This provides a list of possible competitors, collaborators, and/or potential M&A opportunities.
- A go-to-market strategy for launching their product commercially. This includes guidance on maximizing relevant selling features and identifying best-fit marketing forums (conferences, webinars, publications, etc) as well as proof-of-concept data packages for each recommended forum.
- Identifying a target customer profile: companies that are most likely to consider adopting the product, likely decision-makers, and profiles of those who will be using the technology. This process includes a consideration of selling points and related messaging points.
- A revenue forecast model, including assumptions arrived at through the exercises above.

The Impact

Dark Horse provided this client with a one-stop shop for market research, due diligence on expansion opportunities...and a guiding vision of the science and technical questions necessary to create an accurate to-market strategy. Unlike a traditional market research firm, Dark Horse brings centuries of expertise in the CGT field to bear when considering the competitive landscape, competitive advantages, and target customer profiles.

Revenue Forecast for Technology Platform X



Having market research completed by a company with extensive technical experience in the market in question in what distinguishes Dark Horse from other possible sources for market research.

Comprehensive Analytical Support Package for Licensure

Why DHC?

- Expand Client Bandwidth
- Provide Additional Technical Expertise
- Solve Existing Problem (Remediate)

The Ask

In CGT, analytical methods (and the ways in which we apply them) carry even more weight than they might for a standard therapy due to the high level of complexity inherent in C&GT products. Add in the complexities of development in multiple global jurisdictions with different requirements simultaneously, and the required resourcing for analytical characterization of many C&GT products often approaches (or even exceeds) that needed for manufacturing. This late-stage cell therapy client was preparing to file their licensing applications for a product that was currently in multinational clinical trials. DHC provided a broad scope of analytical guidance, ranging from high-level strategic planning of the licensure-enabling analytical strategy to the tactical execution of specific critical tasks.

Service Domains

DHC's Approach

Dark Horse offers varying levels of analytical support, ranging from high-level strategic oversight to detailed tactical operational support. As with all of our services, these options are *à la carte*, customizable to each client and each situation so as to optimally complement the client's internal capabilities and bandwidth. In this case, DHC's support included the following:

- Establishment of a potency assay, including providing guidance regarding overall strategy and rationale for mechanism of action, reduction to practice and method validation, and assistance in drafting and review of related study protocols and reports
- Establishment of other release and characterization methods, including reduction to practice and method validation, and assistance in drafting and review of related study protocols and reports
- Establishment of specifications and associated acceptance criteria for raw materials, drug substance, and drug product
- Establishment of a defined stability program for raw materials, drug substance, and drug product, including providing guidance around setting retest/expiry periods and data trending for shelf-life projections
- Providing guidance regarding strategy and approach for comparability, and assistance in review of related study protocols and reports
- Review of testing plan for delivery device suitability study
- Drafting and/or review of relevant CMC sections for regulatory submissions
- Preparation for and participation in communications with external stakeholders

The Impact

Text Dark Horse's breadth of analytical support on both strategic and tactical matters provided this late-stage program with a wide-angle view of their needs in preparing licensing applications in multiple jurisdictions. Armed with all necessary information, the client was able to accelerate their timeline by making strategically informed and data-based choices about how to use their time/money/personnel most efficiently. An analytical perspective naturally prioritizes long-term thinking, which in this situation will decrease the likelihood of delays as the client proceeds towards commercialization.

Device Development Regulatory Support

Why DHC?

- Expand Client Bandwidth
- Provide Additional Technical Expertise
- Solve Existing Problem (Remediate)

The Ask

When a company develops a product such as an instrument and/or consumable for use in a cell and gene therapy process, one of the steps is to get that product approved for its intended use. In this case study, a client requested regulatory guidance for assistance in achieving this step.

Service Domains

DHC's Approach

First, we ensured a thorough understanding of the core technologies in question by extensively reviewing technical documentation and speaking at length to the development team.

Then, we generated a list of regulatory references as well as a statement of intended use. This material was reviewed in tandem with the client's development team.

If further development or higher volume manufacturing would be required, we have the ability to assist in identifying engineering groups and manufacturing partners.

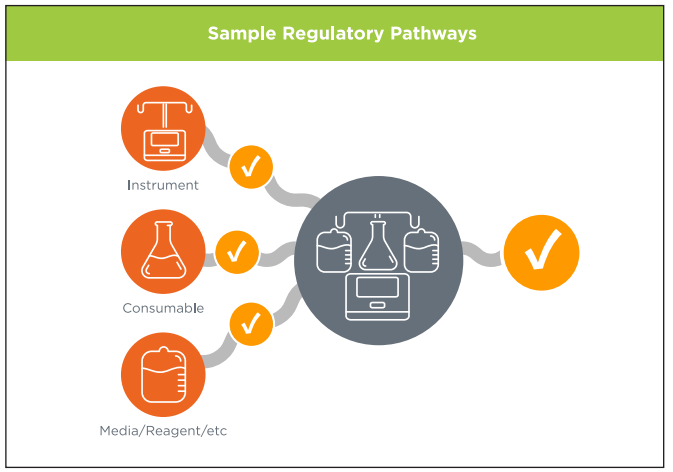
During #2 above, we identified the potential regulatory pathway(s) to approval, including development of the quality system that would be required for the product.

After identifying the types of verification testing and validation testing that would be required for the product, we wrote and executed studies on behalf of the client.

The next step was to meet with the regulatory agency and submit any necessary regulatory documentation. The combination of an instrument with a consumable increases the scope of regulatory requirements needed, with minimal overlap in testing and documentation (as demonstrated in the sample pathway illustrated here).

The Impact

Text The client cleared the regulatory hurdle(s), allowing for their equipment to be utilized in accordance with its intended use in the manufacturing process of a Cell or Gene Therapy.



Landscape Scan of Investment Opportunities in CGT Tools and Technology

Why DHC?

- Expand Client Bandwidth
- Provide Additional Technical Expertise
- Solve Existing Problem (Remediate)

The Ask

DHC is uniquely positioned to identify attractive investment opportunities in the CGT space through integration of our detailed understanding of CGT technologies, regulatory requirements, industry trends, and business and intellectual property considerations. In this case, an investor client requested DHC's assistance in identifying potential investment targets within the CGT Tools and Technology space that were aligned to their investment thesis.

Service Domain

DHC's Approach

First, DHC compiled a "long list" of ~100 tools and technology companies active in the CGT space.

Next, the working team performed a high level scan to identify a "short list" of high priority targets based on high level financial and technical considerations using internal DHC knowledge, in addition to company websites and other publicly available information.

The prioritized "short list" targets were assigned to DHC Subject Matter Experts in their particular market segments for evaluation based on a predetermined, standardized scoring system designed to evaluate technical, market, and strategic considerations.

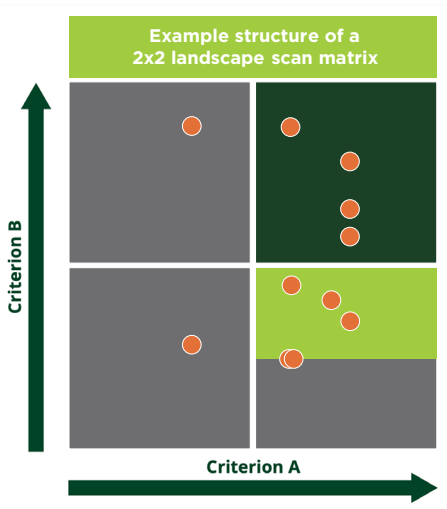
A subset of the "short list" targets also underwent an intellectual property (IP) review by DHC's IP Practice Expert, based on an assessment of the likely importance of IP protection for establishing their 'competitive moat.' The IP review evaluated breadth of claims, global reach, remaining patent term, and licensing status for key intellectual property protecting core assets of the target entities. The results of the IP review were integrated with other market considerations such as potential market stickiness and/or name recognition of the technology to develop an overall view of the target companies' competitive position.

A final assessment included a detailed review of each company, complete with quantitative scoring that ranked each target on two orthogonal criteria of importance for the investment thesis. Ultimately, a dozen potential investment targets were provided to the client, bucketed into two different investment categories.

A review of this complexity often, counter-intuitively, eventually boils down to an unexpected clarity of choice.

The Impact

The client received a summary presentation outlining key data for all "short list" targets, as well as a quantitative ranking of each target on a 2x2 matrix. This provided the client with a dozen potential candidates for consideration, as well as a quantitative assessment of the pros and cons of each entity. In addition to the summary presentation, detailed back-up information was provided in the form of a spreadsheet database of company information and brief IP summary memos on each entity for which an IP analysis was performed.



Technology Transfer and Person in Plant (PiP) Manufacturing Support

Why DHC?

- Expand Client Bandwidth
- Provide Additional Technical Expertise
- Solve Existing Problem (Remediate)

The Ask

For technology transfers, the devil is in the details. The client requested DHC's assistance in managing dose preparation training of clinical sites during international tech transfer of their flagship cell therapy program.

Service Domain

DHC's Approach

- To ensure that the tech transfer would adhere to GMP standards, Dark Horse employed a kitting strategy for dose preparation assembly, put additional controls in place, matched GMP safety-testing techniques, and worked only with appropriately qualified medical technicians.
- The DHC PiP began on-site in the original location for a rigorous train-the-trainer exercise: multi-part training on the dose preparation method.
- DHC then worked with supply-chain vendors for part-matching, temperature control, supply payment, international regulations for tech transfer, and subject matter expert review and confirmation.
- DHC also contracted with a rigorously vetted FACT (Foundation for Accreditation of Cellular Therapy) lab that would ultimately be responsible for the dose preparation.
- The PiP began the process of the same multi-part training—this time, at the FACT lab with the technicians who would ultimately be performing the dose preparation for each patient. In order for an operator to complete the training satisfactorily they had to demonstrate that they could perform each element consistently and to GMP equivalent specifications.
- To support operational consistency throughout the entire process, the DHC PiP trained operators to package the doses for shipping, confirmed courier capacity and temperature-control procedures for transit to clinical sites, and trained those clinical sites and their medical professionals to ensure correct receipt and usage of the final product.
- Once dose preparation, transit, and clinical-site training were completed, the final procedures and expectations were documented and transferred back to the client so that they would remain operationally self-sufficient.

The Impact

Working with Dark Horse provided the client with a highly successful (and reproducible) tech transfer—without loss of even a single batch. The client was able to move forward independently, assured of documentation, training procedures, third party vendor relationships, and supply chain agreements that allowed for an easy transfer of responsibilities.

Project & Program Management, Clinical Stage Cell Therapy

Why DHC?

- Expand Client Bandwidth
- Provide Additional Technical Expertise
- Solve Existing Problem (Remediate)

The Ask

Successful execution of Cell & Gene Therapy clinical trials requires proactive management of a myriad of cross-functional program details. A clinical stage cell therapy client requested DHC's assistance with project management at the interface of CMC and clinical operations.

Service Domains

DHC's Approach

Dark Horse had previously provided support for technical writing of CMC sections of the client's IND submission. Following IND clearance, the client requested DHC's support in the area of project & program management, with a focus on activities at the interface of CMC and clinical, including:

1. Supply chain management activities, specifically: clinical kitting. DHC managed the third party vendor relationship for manufacturing, ordering, and courier activity to various clinical sites for site initiation visits (SIVs).
2. Program and Alliance Management support for the client-CMO relationship. DHC provided project oversight to ensure timely progression through engineering runs and clinical manufacturing.
3. Ongoing cross-functional CMC support between CMC manufacturing and clinical operations. In C&GT this process requires more flexibility than in other spaces. DHC support provided a nimble overhead and pre-production activities schedule to ensure readiness for beginning treatment as quickly as possible once patient(s) were identified and available.

The Impact

The client secured an immediate resource with deep subject matter expertise able to factor in nuances around the client's own needs and engagement with a third party manufacturer. By hiring DHC (vs. an in-house FTE) the client was able to access a contingent, highly-skilled on-demand workforce, able to achieve results unusually quickly and with minimal onboarding time. This flexible ongoing support helped the client get and stay on track with on-call specialists at the ready.

Example Gantt for CMO startup

#	Title	YEAR 1			YEAR 2		
		Q2	Q3	Q3	Q1	Q2	Q3
0	**CMO Program Start-Up Gantt**	CMO Program Start-Up Gantt					
1	Signing Date	Signing Date					
2	CMO Internal Document Drafting	CMO Internal Document Drafting					
3	Cleanroom Suite Turnover Activities	Cleanroom Suite Turnover Activities					
4	**Production & Testing Tech Transfer**	Production & Testing Tech Transfer					
5	TT Run 1 - "I Do" Wet Run at CLIENT Site	TT Run 1 - "I Do" Wet Run at CLIENT Site					
6	TT Run 2 - "We Do" in Cleanroom Suite	TT Run 2 - "We Do" Wet Run in Cleanroom Suite					
7	TT Run 3 - "You Do" in Cleanroom Suite	TT Run 3 - "You Do" Wet Run in Cleanroom Suite					
8	**Engineering Runs**				Engineering Runs		
9	ENG Run 1 - Production & Testing				ENG Run 1 - Production & Testing		
10	ENG Run 2 - Production & Testing				ENG Run 2 - Production & Testing		
11	**Clinical Readiness Activities**				Clinical Readiness Activities		
12	Process Qualification Run				Process Qualification Run		
13	Aseptic Process Stimulations				Aseptic Process Simulations		
14	Clinical Manufacturing Readiness				Clinical Manufacturing Readiness		

Voice of Customer Survey for Cell Therapy Raw Material

Why DHC?

- Expand Client Bandwidth
- Provide Additional Technical Expertise
- Solve Existing Problem (Remediate)

The Ask

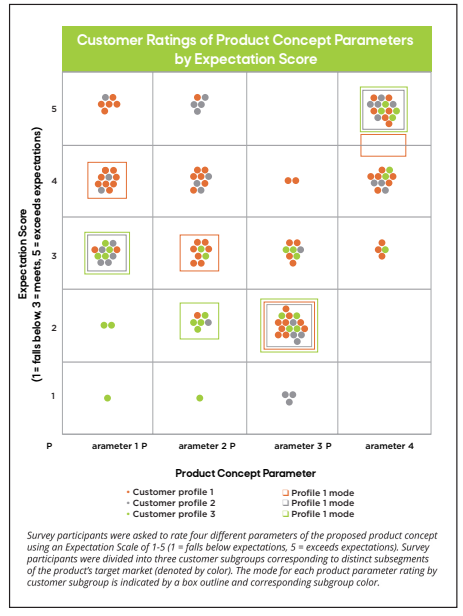
This client had identified an opportunity for offering higher quality raw materials for cell therapy manufacturing and was interested in gathering information about the current and future market expectations to both pressure-test and guide the business opportunity.

Service Domain

DHC's Approach

DHC and the client jointly determined that a Voice of Customer survey of cell therapy developers would best address the parameters that should be taken into account when considering the raw material needs of the potential market. These parameters included the projected demand for the raw materials, manufacturing and testing requirements, variations in the product offering that would appeal to distinct market subsegments, and what kind of characterization data might interest a future customer. The steps taken to complete the project were as follows:

1. DHC evaluated capabilities and expertise of the client to develop a full picture of what the client would eventually be prepared to offer.
2. The client and Dark Horse worked together to craft an appropriate interview guide (set of survey questions) to address current and projected future needs for the raw materials, as well as the criteria to be considered. DHC's diverse experience in cell therapy manufacturing processes and innately deep understanding of these processes provided an unmatched depth and accuracy to these questions.
3. DHC reached out to our extended network of cell therapy experts and potential future consumers of the new product offering. Note the symbiotic nature of this experience: DHC's contacts are an extremely accurate targeted subset of potential clients, meaning not only is the market research on point, but the beginnings of a manufacturer/client relationship is being seeded during the market research process.
4. Dark Horse compiled the survey and completed the first stage of the process: an online survey to capture the quantitative elements in question.
5. That survey was followed by detailed customized in-person interviews to allow gathering of further, highly targeted information. Dark Horse's market researchers are scientists speaking to scientists. This shared language and understanding of the CGT space enhances confidence and is simply more enjoyable and fruitful for all parties concerned.
6. DHC compiled information from the online surveys and interviews, including statistical analyses run on the quantitative answers.
7. Client received a written report and presentation summary overview of all information obtained, in addition to strategic recommendations and a detailed list of key factors to consider.



Survey participants were asked to rate four different parameters of the proposed product concept using an Expectation Scale of 1-5 (1 = falls below expectations, 5 = exceeds expectations). Survey participants were divided into three customer subgroups corresponding to distinct subsegments of the product's target market (denoted by color). The mode for each product parameter rating by customer subgroup is indicated by a box outline and corresponding subgroup color.

The Impact

The client's vision and next steps came into alignment, with a thorough understanding of the opportunity available in light of the needs and expectations of the target customer.

Global CMC Regulatory Strategic and Operational Support

Why DHC?

- Expand Client Bandwidth
- Provide Additional Technical Expertise
- Solve Existing Problem (Remediate)

The Ask

Clinical development of cell and gene therapy products is increasingly an international endeavor, requiring an integrated global perspective. An early stage *ex vivo* gene therapy client requested support with regulatory strategy and the technical writing of filings in multiple jurisdictions.

Service Domains

DHC's Approach

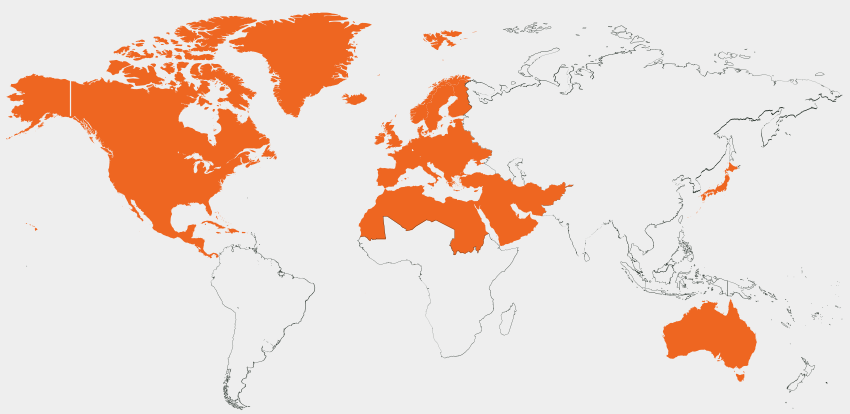
This client was interested in expanding clinical development of their products from a single site academic trial to a multicenter global trial. Each global jurisdiction has specific requirements due to varying governmental regulations. DHC's extensive experience around the world provided knowledgeable support and experience in preparing the technical documents and regulatory filings as well as setting up the regulatory meetings in each jurisdiction.

DHC initially supported the client with regulatory strategy and technical writing of a CMC amendment to support process changes designed to facilitate global manufacturing implementation and improve commercial viability of the existing manufacturing process. That amendment required a comparability study: see pages 18, 32, and 38 for other comparability examples. Following that stage, simultaneous filings allowed for expansion of the trial across multiple global jurisdictions concurrently. During this process, DHC supported the client in preparing IND, IMPDs, and amendments in a wide range of global jurisdictions spanning North America, the Middle East, the EU, and East Asia.

The Impact

All filings to date have been accepted with no delays. DHC strategic and operational support across other fronts (comparability and manufacturing) simultaneous to the regulatory filings streamlined the international regulatory process, leading to faster approvals, financial savings, and the opportunity to support significantly more patients in need of therapy.

Regulatory filings, by region



Market Analysis for a Manufacturing Reagent

Why DHC?

- Expand Client Bandwidth
- Provide Additional Technical Expertise
- Solve Existing Problem (Remediate)

The Ask

This client was considering acquisition of a company with a critical reagent used in the manufacture of viral vectors. To understand the market opportunity, DHC was asked to estimate current and future market sizes for this material as it pertained to its use in Adeno-Associated Virus (AAV) and Lentiviral Vector (LVV) manufacturing processes. This market size assessment was one piece of a broader diligence project conducted for this client. (Find examples of diligence case studies on pages 9, 33, and 37.)

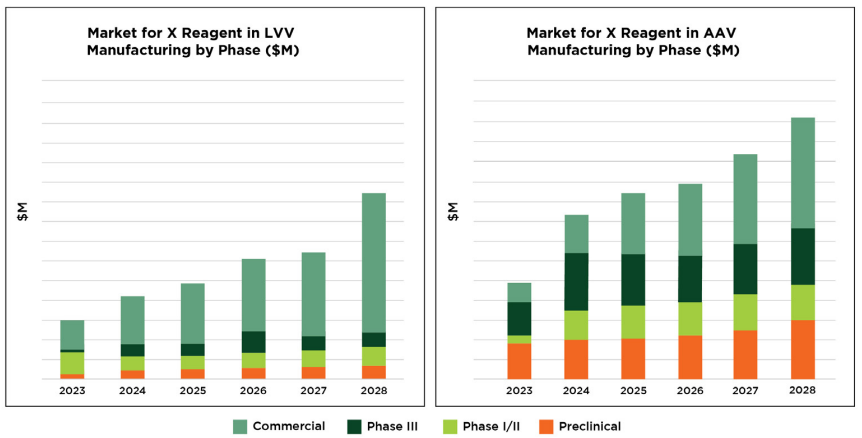
Service Domain

DHC's Approach

- **Alignment of critical assumptions:** DHC compiled key assumptions, including: % of the AAV and LVV markets using this reagent, common price points, and volume requirements of the reagent in standard manufacturing processes. Confirmation of assumptions can be done in collaboration with the client's previous research (if desired) and often requires a combination of literature research and leveraging DHC's network of in-house SMEs who have direct experience with these products.
- **Clinical forecasting:** We leveraged external databases to confirm the current number of relevant CGT programs in development using these two vectors, and forecasted that forward for a 5-year period.
- **Patient population:** Our internal modeling capabilities provided an accurate current and approximated-future estimate of the total number of patients being treated using AAV and LVV, and this was used to calculate the amount of vector required to treat that total expected patient population over time.
- **Market demand:** The total patient population and estimated vector required per patient and in total were used to calculate an estimate for total volume of reagent required to serve the market over the forecast period.
- **Market size:** Our project calculated the overall size of the market based on a range of estimated reagent volume requirements and price points, over the forecast period.

The Impact

In addition to providing comprehensive diligence support, DHC provided a detailed overview of market size for the reagent in question to build a better understanding of whether this potential opportunity aligned with the client's investment thesis. The analysis performed provided the necessary details—including a consideration of the magnitude of potentially obtainable market share for this target—to allow the client to make a solid data-driven decision on future investments.



Strategic Support for Next-Generation CGT Platform

Why DHC?

- Expand Client Bandwidth
- Provide Additional Technical Expertise
- Solve Existing Problem (Remediate)

The Ask

The client asked for a review of the development status of equipment and disposables in addition to the projected timeline for the manufacture and readiness of GMP ready systems with the output being a gap analysis and recommended remediations.

Service Domains

DHC's Approach

- First, DHC reviewed the foundational requirements documents (URS, FRS, SRS etc.) for the system design to check for maturity, clarity, and conciseness, as well as any duplication, all by way of ensuring that requirements were testable and traceable/ trackable to a verifiable source.
- Next, the team studied the project GANTT chart with the client's PM to thoroughly understand the reported status to promised timelines and management's future expectations at a sub-system and system level for the program.
- With an understanding of the development baseline and the upcoming milestones, our team performed a deep dive into the status of each of the development disciplines with the respective design leaders including an assessment of the maturity of the system design: assessing the existing prototype equipment and consumables as well as the proposed changes for inclusion in the next generation system.
- Our review also included a resource assessment to map required effort with the current company resource profile.

The Impact

The client received a gap analysis and an action list, with detailed supporting analysis and recommendations identifying specific remediation necessary to achieve their challenging launch timetable.

Quantitative Modeling of Cell Therapy Mfg Capacity

Why DHC?

- Expand Client Bandwidth
- Provide Additional Technical Expertise
- Solve Existing Problem (Remediate)

The Ask

Predicting manufacturing capacity needs for a pipeline of Cell & Gene Therapy products is an exercise with high stakes and enormous uncertainty. A large biotechnology company came to Dark Horse for assistance in identifying the manufacturing facility needs of its cell therapy product pipeline in the face of a wide range of development and commercial assumptions.

Service Domains

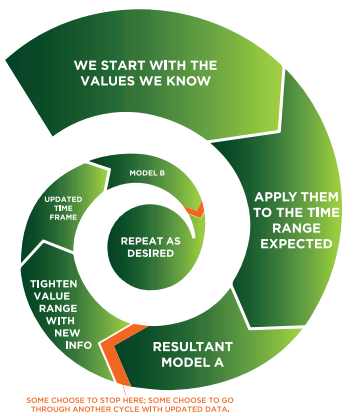
DHC's Approach

The modeling software Dark Horse uses is a proprietary, in-house offering, built specifically from the ground up to factor in the many complexities and variables inherent to the C&GT industry.

As with any model, the output will only be as good as the inputs. DHC's platform has been designed to capture the breadth of input assumptions, such as materials costs, process duration and yield, clinical enrollment, probabilities of success, and timeframes for each phase of development. Our platform then simulates the range of potential outcomes with distributions and Monte Carlo algorithms. Identifying the range for these parameters can be daunting, but our team is equipped to provide help based on process specifics and industry standards. Our platform provides the full range and probabilities of outcomes, making it easier to develop strategies based on risk and control.

- The first step necessary (from the client) is a completed questionnaire to help nail down all known elements and variables. Again, DHC can provide levels of help and guidance in completing this assessment, depending on each client's need.
- DHC then takes those initial variables and uses them to build a highly customized model using our proprietary in-house platform. Check-in meetings are scheduled every week or two for updates, to show interim data, and to alert the client to any places where the model requires more information or where there's conflicting guidance from within the organization.
- The ultimate deliverable is an excel file and a presentation, complete with a dashboard that highlights major outcomes and walks users through the steps taken. This dashboard allows clients to update input parameters to keep the model current and customized throughout the process.
- The ability to model uncertainty is one of the elements that make Dark Horse's quantitative model offering different. We account for ranges so that you can make a plan and, critically, that plan changes with your real-time experiences because it allows for an adaptive approach. It's the difference between a 2D view of the range of outcomes...and a 4D one.

Forecast by Design



We use Quality by Design (QbD) elements in nearly all of our engagements, meaning that the process and manufacturing used are developed to allow for continual evolution. Think of our proprietary quant modeling software and resultant capabilities as a Forecast by Design (FbD). In other words, we don't simply take the known variable and apply them...we instead use a neutral real range of numbers and the ability to revise/pivot the model to eliminate guesswork at each stage, and continually improve forecasts.

The Impact

The client received a highly-customized, probability-weighted picture of the likely range of capacity needs and manufacturing costs for its cell therapy product pipeline, based on Monte Carlo modeling of a range of input assumptions. This hard data provided them with the ability to make rational choices in their facility design process, as well as to increase the accuracy of their financial forecasts.

Nonclinical Comparability Testing

Why DHC?

- Expand Client Bandwidth
- Provide Additional Technical Expertise
- Solve Existing Problem (Remediate)

The Ask

In vivo comparability testing, when required, can be difficult to design and execute optimally. A cell therapy client hired DHC to design and outsource nonclinical efficacy and safety studies to demonstrate comparability of a changing clinical stage manufacturing process. This engagement combined two overlapping areas of DHC services: preclinical development and comparability studies.

Service Domains

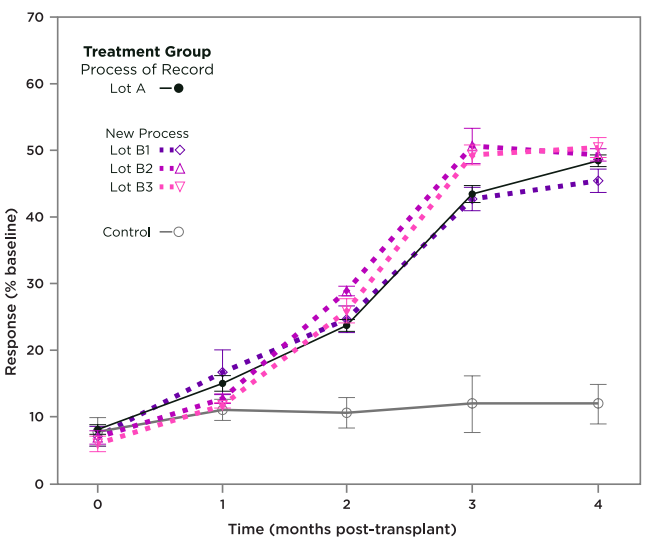
DHC's Approach

- The first step was to evaluate existing nonclinical data and identify the critical efficacy and safety outcome measures required to demonstrate drug product comparability.
- Dark Horse then drafted complete study protocols for the efficacy and safety studies, including documents necessary for IACUC committee review. DHC provided detailed guidance on the study parameters required to meet the project objectives, including (but not limited to): model selection, treatment groups, sample sizes, in-life duration, endpoints, surgical and husbandry expertise needed, and prospective statistical analyses.
- To facilitate study outsourcing, DHC reviewed candidate preclinical contract research organizations (CROs) and provided the client with a list of recommended preclinical CROs weighted by expertise, equipment and housing, timeline and availability, training/oversight needs, and cost.

The Impact

By working with Dark Horse, the client received a clear vision of the nonclinical development path and comparability package needed to support the manufacturing process changes for their clinical stage drug product. Additionally, the client identified and forged relationships with the preclinical CROs best suited to support ongoing development of their cell therapy program.

Comparability Plots: tracking new projects vs. original



Buyer-Side Diligence in CGT Tools & Tech

Why DHC?

- Expand Client Bandwidth
- Provide Additional Technical Expertise
- Solve Existing Problem (Remediate)

The Ask

Diligence in cell and gene therapy (CGT) requires not only the necessary research, but also an integrated in-depth analysis and interpretation of the findings based on a deep understanding of the technical field. This investor client required rapid and thorough diligence on a potential acquisition target (a viral vector tools and tech company) including review and assessment of the potential target's IP portfolio and the competitiveness and relative strengths of its products as compared to the competitive landscape.

Service Domain

DHC's Approach

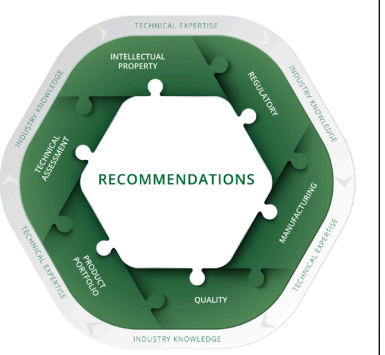
Focusing on the target entity's flagship product, DHC performed a detailed, technical, and IP-driven analysis of the target entity's technology. Our team:

- Evaluated the target entity's patent portfolio for coverage of its commercial and soon-to-be launched products, including claim scope, geographic coverage, and remaining term. We performed a comprehensive deep dive into the IP rights (patents) across the globe, with a particular focus on jurisdictions with a high commercial value.
- Assessed the target entity's "competitive moat" by evaluating and weighting the scope of patent coverage, assessing the relative value of know-how in the field of the target's flagship product, and considering competitors' potential workarounds, technical capabilities, market presence, and market share.
- Further evaluated the flagship product's technical and commercial performance, using, for example, the following tools:
  - a blinded "voice of customer" survey, which assessed customer perception of the company and its flagship product relative to competing products
  - a critical review of performance data (provided by the target company) with a head- to-head comparison of the flagship product with competing products
- Considered intangible factors contributing to the flagship product's market adoption, including the degree of market "stickiness" and the factors in this particular industry that contribute to customer loyalty or lack thereof.
- Provided an objective and unbiased assessment of the target entity's technology within a tight deadline, allowing the client to achieve a high level of confidence within a short deadline for an investment decision.

The Impact

DHC provided the client with a detailed and unbiased assessment of the target entity's technology, including evaluation of the their existing and soon-to-be launched products in the marketplace vis-à-vis competitors' similar products. Our client gained a clearer understanding of the technical capabilities of the target entity and its competitors, their relative positions in the market landscape, the status of the target entity's IP assets, and an assessment of the perceived competitive advantage that the target's flagship product held. The deliverables provided by the DHC team armed our client with a complete slate of information necessary for effective decision-making on the potential investment.

DHC multifaceted approach to buyer-side due diligence



The comprehensive assessment for each potential target in question includes evaluation of technical, financial, regulatory, and intellectual property consideration, enabling a holistic picture of target value.

Process Codification at Early Clinical Phase

Why DHC?

- Expand Client Bandwidth
- Provide Additional Technical Expertise
- Solve Existing Problem (Remediate)

The Ask

Precise definition of a manufacturing process is critical for effective communication with regulators, contractors and partners. A client with an autologous *ex vivo* gene therapy platform requested DHC's assistance in codifying their manufacturing process in preparation for an international technology transfer and global regulatory filings.

Service Domain

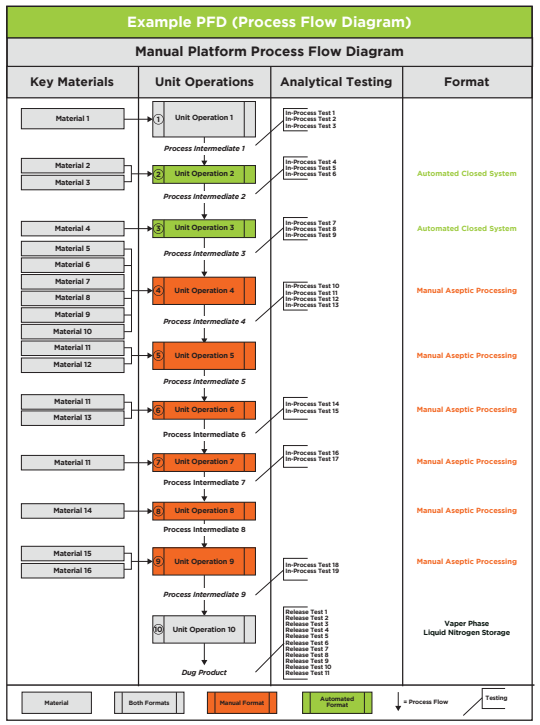
DHC's Approach

DHC's approach to process codification uses a standard set of Quality by Design (QbD) tools such as process flow diagrams (PFDs), Quality Target Product Profiles (QTPPs), and risk analyses to describe the process of creating and the analytical methods used to characterize the therapy in question. As a key step in the process codification process, DHC identifies and distills all elements of the client's CMC into one or more visual representations known as a PFD. A PFD can be produced at any level of detail, from the thirty-thousand-foot view down to an extremely detailed snapshot, depending on need. Tools such as QTPPs and risk analyses further increase understanding of target process characteristics and associated risks to prioritize future development efforts. A statistical data analysis of the manufacturing process data provides a clear understanding of process performance to date, and of any potential correlations between key process inputs (processing parameters) and outputs (analytical results).

The Impact

After process codification this client experienced:

- increased internal clarity around—and deeper knowledge about— the inner workings of their process.
- a more comprehensive ability to communicate process details to external stakeholders, including contract manufacturers (tech transfers) and global regulators (INDs/IMPDs).
- a thorough and logical framework for communication of process changes to regulators during comparability submissions.



Analytical Dev: Evaluation of Candidate Potency Assay

Why DHC?

- Expand Client Bandwidth
- Provide Additional Technical Expertise
- Solve Existing Problem (Remediate)

The Ask

Potency assays should reflect efficacy-associated *in vitro* and *in vivo* activity. The client requested assistance from DHC with the design and use of nonclinical studies to demonstrate biological relevance of their lead candidate *in vitro* potency assay for a clinical stage cell therapy product. This interaction demonstrates a common industry overlap between the service areas of analytical and preclinical/nonclinical development.

Service Domains

DHC's Approach

- The goal of this project was to obtain proof-of-concept *in vivo* data to support the validity of the client's *in vitro* potency assay and to set assay acceptance criteria that could be used to evaluate the lot-to-lot consistency of the client's drug product.
- Dark Horse's extensive experience in nonclinical modeling and *in vivo* mechanistic studies provided the necessary know-how to identify a viable strategy for establishing the physiological relevance of the client's *in vitro* potency assay.
- The first step was to evaluate existing nonclinical data and identify potential strategies to demonstrate causality between the cell therapy product's activity in the candidate *in vitro* potency assay and the product's *in vivo* therapeutic activity.
- Once an optimal strategy had been selected, DHC provided the client with a detailed design of the proof-of-concept *in vivo* nonclinical study, including key outcome measures and a sampling plan that would allow the program to advance beyond correlation and demonstrate a causative role of the product's hypothesized therapeutic mechanism of action.

The Impact

The outcome of this engagement was the identification of the strategy necessary to verify the physiological relevance of the lead candidate potency assay for a clinical stage cell therapy product.

Device Dev for Cell Therapy Manufacturing Equipment

Why DHC?

- Expand Client Bandwidth
- Provide Additional Technical Expertise
- Solve Existing Problem (Remediate)

The Ask

Development of novel cell therapy products occasionally requires bespoke solutions to overcome manufacturing or product delivery challenges. In this case, a cell therapy client wanted to increase the scalability and cost-effectiveness of manufacturing of their drug product by identifying a closed and automated solution for a manual, laborious, open processing step.

Service Domains

DHC's Approach

- DHC'S first step was to define the URS (User Requirement Specifications) to ensure that all needs were taken into account. During this process, DHC worked with the client to weight their needs to identify what matters most and why, ensuring an ultimate selection that prioritized the most urgent or required needs.
- DHC conducted a landscape assessment of potential design and technological improvements which could potentially be make to the manufacturing process. DHC utilized expertise in customer device development and process development to propose several existing and custom device and equipment concepts. The client then selected one of the custom concepts that they believed would best fit their needs.
- DHC generated a RFP (Request for Proposal) which detailed the User Requirements for the custom device and equipment concept. DHC identified and vetted Contract Engineering Groups (CEGs)—those which had the necessary design expertise and experience in the custom device and equipment development—and submitted the RFP to those determined to be possible best fits for the scope of the project.
- The proposals that were received from each of the CEGs were analyzed, additional information was requested as needed, and project negotiations were initiated. Information collected from the proposals and visits were compiled into a presentation providing a detailed analysis of which CEGs would be the best fit.
- Throughout the custom device development process, DHC generated test protocols and reports that identified design specifications and process parameters through the use of Design of Experiments (DoE).
- Dark Horse was also responsible for V&V (verification and validation) testing, including biocompatibility, extractables/leachables, sterilization, shelf life, and user validation. DHC identified appropriate vendors, generated the test protocols/ reports, and coordinated the execution of all studies.
- DHC provided a regulatory assessment based on the intended use of the custom device and equipment. DHC then served as the lead author of the submission to the target regulatory body which included coordination with both the client's regulatory team and the Contract Engineering Group.

The Impact

Through the combined efforts of DHC and the CEG, the client received a turnkey solution to address their requirements, from initial design selection to implementation.

Due Diligence of Phase III Readiness for Cell Therapy

Why DHC?

- Expand Client Bandwidth
- Provide Additional Technical Expertise
- Solve Existing Problem (Remediate)

The Ask

CMC is frequently on the critical path for cell and gene therapy product development timelines. A venture capital firm requested a rapid evaluation of CMC Phase III readiness for a cell therapy asset in which they were considering investing.

Service Domains

DHC's Approach

In this case, the review of the asset had eight components. The review took into consideration Phase III readiness as well as next steps that would be necessary for suitability for BLA (Biologics License Application). Over the course of a fast-tracked three week review, DHC performed:

1. A process-trending and reproducibility analysis of the company's manufacturing process based on historical records of previous batches in Phase 1 and Phase 2.
2. A raw material suitability analysis, considering the materials' fitness for both late stage and commercial manufacturing.
3. A review of the facility's QMS (quality management system), in addition to projecting forward to identify future gaps in commercial readiness.

   In many cases, Quality Systems support is not a stand-alone project, but instead an element that appears to varying degrees throughout another project. In the case of this example, we see a QMS-readiness review making an appearance: both conceptually, and as part of a follow-up on-site audit (#3 above & #7 below).
4. An analysis of the facility's qualification status and validation master plan.
5. A review of the development status of critical in-process and release assays used to characterize the product.
6. A review of all recent FDA correspondence with a particular eye to any potential issues that could impact Phase III initiation and/ or BLA approval.
7. An on-site quality and technical audit to determine Phase III readiness and PAI (pre-approval inspection) readiness of both the manufacturing facility and quality management systems.
8. The writing/delivery of a final report summarizing all identified risks to Phase III readiness. Within the report, each element was given a risk rating (critical – significant – moderate – minor) which takes into account anticipated time and a rough cost estimate for remediation if necessary. Recommended timing and approach for remediation were provided for each item. Additional recommendations were provided regarding next steps for items with little risk for Phase III readiness, but that would require remediation prior to BLA.

The Impact

Within three weeks of start, the client had in hand a report enabling them to make an informed investment decision and providing a post-investment roadmap to Phase III and commercial CMC readiness.

Comparability Package to Demonstrate Mfg Equivalence

Why DHC?

- Expand Client Bandwidth
- Provide Additional Technical Expertise
- Solve Existing Problem (Remediate)

The Ask

As manufacturing processes are refined and scaled, demonstration of product comparability is critical. An established biotech advancing a gene-modified cell therapy platform requested DHC's support in demonstrating comparability of their improved manufacturing process and streamlining associated filings with global regulators.

Service Domains

DHC's Approach

In this case, the client was implementing two manufacturing changes (detailed below) while simultaneously preparing to open a multi-jurisdictional clinical trial.

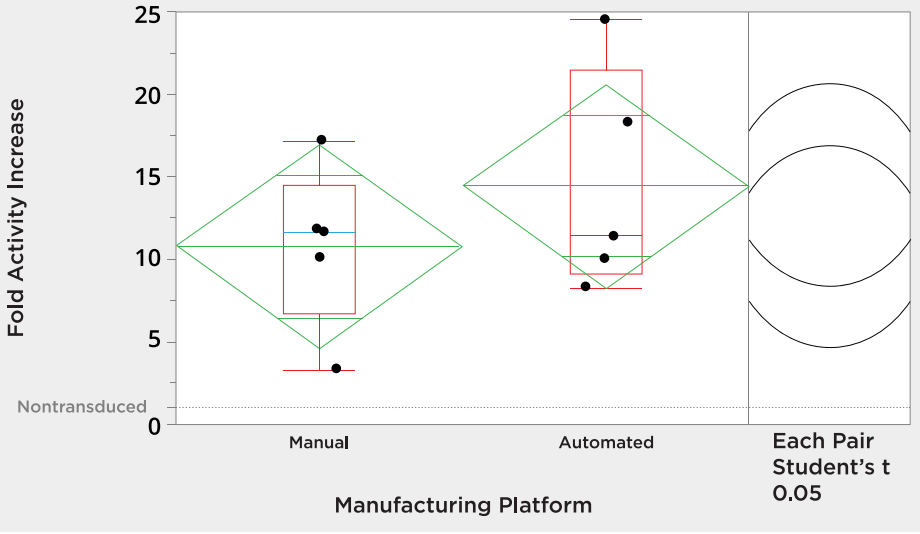
- Initial patient therapeutic dosages were created using a manual process. For this autologous therapy, achieving improved consistency and reducing cost of goods became possible through a shift from a manual process to an automated process.
- To optimize safety, performance and consistency, the client improved the viral vector being used to deliver the gene therapy.

Various considerations including time, cost, and feasibility constrained available study designs to demonstrateequivalency between the old and new processes. DHC worked with the client to design the comparability study plan, analyze the resulting study data, and write up the study findings for submission to global regulators.

The Impact

DHC's strategic design of the comparability package and tech writing for the regulatory submission allowed for a quick and cost-effective proof of equivalence. The comparability submissions were accepted by global regulators with limited questions, resulting in delay-free implementation of the improved manufacturing methods in multiple global jurisdictions.

Manual vs. Automated System Comparison



Manufacturing Support in CDMO Selection Process

Why DHC?

- Expand Client Bandwidth
- Provide Additional Technical Expertise
- Solve Existing Problem (Remediate)

The Ask

For companies choosing to outsource manufacturing, selection of the right CMO (Contract Manufacturing Organization) is critical. The client requested DHC's assistance in selecting a CMO that would provide a clear path through commercialization for their preclinical stage gene therapy program.

Service Domains

DHC's Approach

- DHC's first step was to define the URS (User Requirement Specifications) to ensure that all needs were taken into account. During this process, DHC worked with the client to weight their needs to identify what matters most and why, ensuring an ultimate selection that prioritized the most urgent or required needs.
- Then, DHC put together a detailed RFP (Request for Proposal) to send out to CMOs who were likely fits for the clients' needs. The process of creating the RFP always undergoes a series of client reviews until the document is widely agreed to cover all bases, ensuring that CMOs in consideration have a complete and transparent understanding of the project requirements.
- DHC recommended a short list of RFP recipients based on in-depth knowledge of various CMO's strengths, timelines, availability, etc., as well as consideration of the clients' eventual regulatory expectations. In this case, the RFP went out to five CMOs that met the requirements, in a process parallel to an assessment of the academic CMO that was currently in use.
- DHC actively managed the CMO selection process to expedite decision making. Once RFP responses were returned, DHC used a proprietary RFP evaluation system to turn the qualitative answers into a quantitative measure of each CMO's likely match to client needs.
- In consultation with the client, the initial CMOs were narrowed to two finalists. In-person quality and technical audits were performed for each finalist by DHC subject matter experts, allowing for an in-depth vetting of each manufacturer.
- The client received DHC's executive presentation summarizing the strengths and weaknesses and ultimate recommendations, discussed the results with DHC consultants, and made a decision.

The Impact

The output of this project was the selection of a CMO that would meet the client's needs both today and in the future. DHC was able to deliver on the client's need for a rapid decision-making process by assessing manufacturers on parallel tracks, receiving expedited responses (due to both reputation and industry relationships), and leveraging prior experience to speed RFP preparation and response review. Ultimately, the impact for the client was the identification of and beginning of a relationship with a CMO that will suit their needs for years to come.

Our Service Domains

CMC

REGULATORY

NONCLINICAL

CLINICAL

QUALITY & COMPLIANCE

BUSINESS ANALYTICS

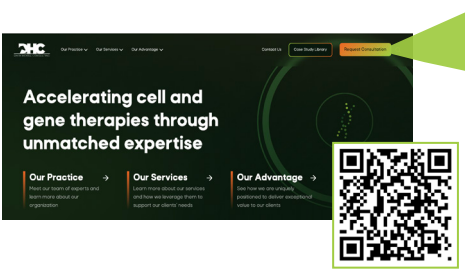
Above, you see our six **Service Domains.** To demonstrate what you might experience as a Dark Horse client, **we've put together case studies to showcase concrete examples of some of our engagements.** All case study examples are taken from real-world client experiences but are blinded to protect confidentiality.

All case studies follow a pattern. We describe the client's need **(The Ask),** a summation of the steps we took to complete the work **(DHC's Approach)**, and the result of the engagement **(The Impact).**

Common reasons that a client may request to work with DHC include needing the depth of our technical expertise, additional bandwidth to support their in-house teams, and/or assistance with remediation. In our **"Why DHC?"** visual we demonstrate the degree to which each of these apply.

All of our services and engagements are customized to each client's needs, so please consider each case study to be a jumping-off point for your consideration.

This QR code will take you to our case study library,
the repository of this ever-growing set of use-case examples. We show them in reverse chronological order, so the newest release will always be at the top. This online library can be filtered by Service Domain, Client Type, Stage, and Modality.



Visit darkhorseconsultinggroup.com/consult/ or scan the QR code to request a complimentary initial consultation. We look forward to working with you.

DARK HORSE CONSULTING

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