Northwest Biotherapeutics: CEO Linda Powers' Brilliant Manufacturing Strategy Has Created Enormous Shareholder Value

Posted *by* Larry Smith *on* Apr 11, 2023 • (**0**)

Acronyms Used in This Report

MHRA **M**edicines and **H**ealthcare products **R**egulatory **A**gency is the United Kingdom regulatory counterpart to FDA. The two agencies have a close, collegial working relationship. Approval of DCVax-L by MHRA would carry great weight in the FDA's decision making

GMP **G**ood **M**anufacturing **P**ractice is a system required by regulatory agencies for ensuring that drugs are consistently manufactured according to carefully defined quality standards. Guidelines address issues such as process validation, quality assurance assays, record keeping, personnel qualifications, sanitation, cleanliness, equipment verification and others.

MIA **M**anufacturer's **I**mportation **A**uthorization is required by the MHRA before a company can manufacture, import or export drugs. To qualify, a manufacturer needs to demonstrate to MHRA that it complies with good manufacturing practices and can pass regular GMP inspections of its manufacturing site.

MAA **M**arketing **A**uthorization **A**pplication is the document that must be submitted to the MHRA (and other European regulatory agencies) by companies seeking approval for a drug. The MIA is an integral part of this submission. Approval of the MAA allows commercialization.

BLA **B**iologics **L**icense **A**pplication is the document that must be submitted to the FDA by companies seeking approval to market a biologic product in the US. It is comparable to an MAA.

CDMO **C**ontract **D**evelopment and **M**anufacturing **O**rganization companies provide biopharma companies with comprehensive services ranging from drug development through manufacture. Northwest uses the UK firm Advent BioServices as a CDMO.

GBM **G**lio**b**lastoma **M**ultiforme is the most aggressive and deadly type of brain cancer, ndGBM is newly diagnosed and rGBM is recurrent. These are the two indications initially being sought by Northwest Biotherapeutics for DCVax-L

Overview

This note was prompted by and analyzes the importance for NWBO of the MHRA's recent approval of an MIA for commercial manufacturing of DCVax-L at the Sawston UK facility operated by Advent BioServices. Remember that the facility previously has been licensed for producing DCVax-L for compassionate use. This is a key factor in the brilliant and extremely valuable manufacturing infrastructure that Northwest has put together under the leadership of Linda Powers.

In order to receive MAA regulatory approval of DCVax-L in the UK, NWBO must achieve two critical steps.

- The phase 3 trial must demonstrate a medically significant improvement over existing therapy in nGBM and rGBM, and
- NWBO/ Advent must demonstrate the ability to manufacture the drug meeting GMP standards as detailed in the MIA.

The issuance of the MIA license by MHRA clears one of these major hurdles and is a prerequisite for submitting an MAA.

Executive Summary and Key Conclusions

MIA Approval Is an Outstanding Accomplishment

The MHRA approval of the MIA for the Sawston commercial cell therapy manufacturing facility enables the production of DCVax-L, not only for the UK, but also for other countries as regulatory approvals are gained. Northwest owns the Sawston facility and various

manufacturing patents used in production while Advent BioServices leases and operates the Sawston facility under contract. This is an amazing and extremely important accomplishment for Northwest and Advent, which is a related party to Northwest.

The MHRA has only approved three MIAs for cell therapy with the Northwest/ Advent and one other being recent. Cell therapy manufacturing (especially the personalized living cells used in DCVax-L that vary greatly from patient to patient) is orders of magnitude more difficult than traditional processes for organic molecules and proteins (principally antibodies). This places Northwest and Advent at the forefront of the worldwide cell therapy manufacturing. Why is this so important? For many decades, drug development was focused on organic molecules. About two decades ago, products based on antibodies emerged and are the now the major force driving worldwide pharma sales. The next major growth driver will be products based on living cells.

The value of the Sawston facility to Northwest shareholders is extremely underappreciated. At this early stage of development of living cell therapies, there is a significant lack of manufacturing expertise and of course capacity. Let me illustrate this. Cognate BioServices is a leading contract development and manufacturing organization that is specialized in cell and cell-mediated gene therapies. Charles River Laboratories acquired Cognate in April 2021 for the clearly stated purpose of gaining a strong foothold in cell therapy manufacturing. They paid $825 million. I am not able at this time to do a head to head comparison of Cognate's business capabilities versus that of the Sawston facility. Whether Sawston is worth more or less remains to be determined. **However, it is clear that apart from the strategic importance for DCVax-L production, the value of the Sawston facility could have substantial additional value as a cell therapy CDMO, perhaps in the several hundreds of millions of dollars.** Later in this report, I will touch on NWBO's acquisition of Flaskworks which has a technology that automates and could very meaningfully improve the productivity of Sawston. **Successful future development of Flaskworks could have a multiplier effect on the value of the Sawston plant**.

MIA Approval Greatly Increases the Potential for DCVax-L Approval in the UK

The MIA approval is critical for Northwest because it is a prerequisite for filing an MAA for DCVax-L. It is not infrequently the case that MAAs or BLAs despite having compelling clinical data, are delayed because of problems in demonstrating GMP manufacturing capability. With the MIA approval for commercial manufacturing, this appears to no longer be a meaningful risk. Frankly, my greatest concern about NWBO gaining DCVax-L approval was whether it could meet regulatory requirements for GMP manufacturing. I have long felt that the clinical data for DCVax-L is compelling.

When might the MAA Be Submitted?

Investors are now trying to estimate when the MAA will be submitted and how quickly the MHRA might act to approve it. The document that NWBO will submit is massive. The Company has said that it is around 1.5 million pages. It will likely still require additional time to incorporate the manufacturing and clinical data. Management is not providing any guidance on when it will file the MAA. As a sheer guess, I think it could be around two months or so. I re-emphasize that this is a guess based on my experience that NWBO has been careful and methodical in data analysis and submissions in the past.

How Long Might It Take for MHRA to Review and Hopefully Approve DCVax-L?

I am hopeful that the MHRA will move swiftly with its review. The MHRA has stated its intention to make the UK a world leader in biotechnology drug development by expediting development of drugs that promise a significant advance over existing therapies in treating life threatening diseases. GBM, the initial cancer target of DCVax-L, certainly fits this description. A noteworthy example was that the UK was the first country to approve a COVID-19 vaccine. Pfizer first submitted efficacy data to the MHRA on October 2, 2021 and temporary marketing authorization was granted on December 2, 2021. Obviously, the need for the COVID-19 vaccine was extraordinary. I am not necessarily implying that MHRA will feel the same sense of urgency for DCVax-L. However, it does show that MHRA can move quickly. If the MAA is filed sometime in the coming months, I am guessing that there could be an approval by yearend or early next year. Management has not offered any guidance on this issue.

Manufacturing Capacity Upon Approval

Upon approval, NWBO can quickly spring into commercial production because of the MIA approval. In a December, 2021 press release, Northwest stated that it had developed Phase 1A of Sawston, which comprises approximately 4,400 square feet of the overall 88,345 square feet. The Company anticipates that Phase 1A alone will be able to manufacture DCVax-L products for 45-50 patients per month or 450-500 patients per year; the 450-500 number allows for some downtime for cleaning. Obviously, there is room at Sawston for expansion if demand expands exponentially.

Estimating Price Per Patient Treated with DCVax-L is Not Straightforward

In thinking about pricing per patient, we must first consider dosing. In the phase 3 trial, the prescribed dosing was to give two intradermal injections at days 0, 10, 20, and at weeks 8, 16, 32, 48, 72, 96 and 120 so this would be 20 distinct injections at ten distinct times over two and one-half years. NWBO has not discussed pricing, but we know that new cancer therapies are routinely priced at several hundred thousands of dollars. For example, the exciting new CAR-T cell therapies are priced at $300,000 to $400,000 per patient. Unlike the multiple doses used with DCVax-L, the CAR-T drugs are given in one infusion. They are also associated with severe, sometimes life threatening side effects that usually require hospitalization so that in extreme cases the all in cost to the health care system can be $1 million.

Estimating the price per patient for DCVax-L is not as straight forward as CAR-T cells because it is given in a series of injections. Not all patients will receive 20 injections. If the patient progresses, treatment might be stopped. (Although it should be noted that the phase 3 trial suggested a benefit even in the event of progression.) Also, if DCVax-L is judged to be effective and if there is sufficient drug available, a patient might receive more than 20 injections. At this point in time, I have no good estimate as to how many doses will be received by the average patient.

Of great importance in thinking about pricing is that the side effect profile of DCVax-L is benign, not much different from placebo. This means that the cost of dealing with side effects is virtually zero versus potentially several hundred thousands of dollars for CAR-T. Also, the price of CAR-T therapy is the same for the roughly 50% of patients who receive a meaningful benefit as the roughly 50% who don't receive benefit. In the case of DCVax-L, if the patient does not respond or progresses at some time in therapy, the dosing can be stopped. These are key factors that payors will consider in negotiating reimbursement for DCVax-L.

In looking at the clinical data, my judgment is that the medical benefit afforded by DCVax-L in GBM is comparable to CAR-T therapy in hematological cancers. If payors agree with my analysis, it would follow that payors might find it easier to grant reimbursement that potentially could be $300,000 or even more per patient as they consider the all-in cost of therapy. This $300,000 likely would apply to patients who completed 120 weeks of treatment. Let me re-emphasize that the benign side effect profile and the ability to stop dosing if the patient does not respond to treatment could argue for a price greater than $300,000 per patients who complete the entire 120 weeks course of treatment.

The final point to consider is whether NWBO will establish a fixed price for each injection of cells so that the price of the dose given at any time of treatment is the same. Maybe. However, it might also be the case that the initial doses are priced higher than later doses. Management has not commented on any of these pricing issues.

Projecting Sales in the Early Phase of Commercialization

Upon approval of the MAA, NWBO is now positioned to quickly move to commercial operations. So in the near term, what kind of sales potential might there be? My speculation is that the initial demand will be so great that manufacturing capacity will be the gating factor for sales. Just for the sake of discussion, let's assume that the average price realization per patient over their entire treatment period is $100,000 (this seems very low). This suggests that the Sawston facility with a capacity of 450 to 500 patients per years could initially create a revenue stream of $45 to $50 million spread out over a time period of more than one year. At $200,000 per patient the revenue stream would be $90 to $100 million.

Manufacturing Is Set Up to Meet Future Needs Even If Demand Expands Exponentially

Over time, the current manufacturing capacity at Sawston can be increased many times and is capable of supplying much of the worldwide demand. Currently, DCVax-L production is only taking up 5% of the space at Sawston. NWBO is also far along in developing its highly automated Flaskworks manufacturing technology which has the potential to enormously increase annual production per square foot.

The CDMO Cognate provided the DCVax-L used in the phase 3 trial. It is likely that it will be developed as a second production source. As previously noted, Cognate was acquired by Charles River Laboratories in April 2021 for $875 million.

It is estimated that the annual incidence of GBM in the US is about 12,000 patients. Incidence in Europe is comparable so that these two markets constitute an addressable market of about 24,000 patients. The addressable worldwide market for developed countries is even greater given that there is significant incidence in China, Japan and Australia. If DCVax-L lives up to my expectations, it could l be used in a majority of these patients over the coming years. The Sawston facility and Cognate manufacturing capacity should be able to handle this demand if it emerges.

There will also be the need to supply product for clinical trials in the short and intermediate term. One highly promising example is the combination of DCVax-L with the checkpoint inhibitor Keytruda. A phase 2 trial has suggested that this combination could offer a striking improvement in survival in GBM as compared to DCVax-L alone. The numbers in this trial are small, but the results are very encouraging. These results, if confirmed, could spur numerous trials combining DCVax-L with other oncology agents in coming years.

It is also important to understand that the mechanism of action of DCVax-L will likely be effective for all solid tumors that can be surgically resected. There is evidence of effectiveness of DCVax-L in prostate and ovarian cancer. In coming years, there is the potential for a huge number of trials across the solid tumor spectrum. I would also note that we have seen exciting data in a phase 1 trial of a different type of dendritic cell vaccine, DCVax Direct.

CEO Linda Powers must be given enormous credit for putting together a brilliant manufacturing strategy that gives the solid promise that NWBO will not be supply constrained in the foreseeable future.

Further Discussion of the MIA Approval

MHRA approval of an MIA for commercial cell therapy manufacturing is a prerequisite for MAA submission. Thus, the MIA blessing greatly enhances the potential for UK approval of DCVax-L for treatment of both ndGBM and rGBM.

DCVax-L is personalized dendritic cell vaccine and the end product is a living cell. Products based on living cells are in the very early stages of commercialization. The complexity of manufacturing is orders of magnitude greater than products based on organic molecules and complex proteins (principally antibodies) which are the basis for almost all current drug therapies. This complexity has been recently evidenced by the manufacturing difficulties experienced by Novartis and Bristol-Myers Squibb in the launches of their CAR-T cell therapies. Northwest/ Advent with the MIA approval must now be considered to be at the leading edge of cell based therapy manufacturing. The MHRA has only issued three MIA's for cell therapies, of which the NWBO/ Advent and one other were just recent. The MIA approval would be a proud accomplishment for even the largest of global biopharma companies.

I have felt for several years that the phase 3 clinical data for DCVax-L was compelling. The results have been incredibly well documented and validated, first in a peer reviewed presentation at the New York Academy of Sciences in May 2022. The presenter stated that the phase 3 trial successfully reached its primary endpoints and that DCVax-L was a breakthrough for ndGBM and rGBM. The results were then published in a peer reviewed article in the prestigious medical journal JAMA Oncology in November 2022 . Finally, November 2022 also saw a peer reviewed presentation at The Society of Neuro-Oncology, which is the foremost medical conference in the world for physicians specializing in brain tumors. And importantly, the investigators participating in the phase 3 trial of DCVax-L who have spoken publicly are uniformly supportive of DCVax-L meaningfully extending the lives of many GBM patients they have treated. These provides powerful support for my belief that DCVax-L represents a major advance in treating glioblastoma multiforme in particular and quite probably immunotherapy in general.

While I have been confident in the clinical data being accepted and viewed positively by regulatory agencies, I was very concerned about the ability of NWBO to obtain an MIA. All too often, a small (or large) biopharma company will achieve positive clinical results only to trip up on manufacturing with the result that the company receives a Complete Response Letter (CRL) that delays approval. Given this ominous history and the much greater complexity involved in cell based therapy manufacturing, I was anxious. I let out a huge sigh of relief with the MIA approval.

Further Discussion of the Pending MAA Submission

For all regulatory agencies, the COVID lockdowns have significantly delayed regulatory functions. Against this backdrop, the MHRA moved rapidly to approve the NWBO/Advent MIA. Now, NWBO moves on to the submission of the MAA to MHRA.

The MAA is a complex document which includes both clinical data and the MIA. NWBO stated last December that it was very far along in preparing the MAA and noted that there were around 1.5 million pages in the document, but it still had further work to do and also had to wait for the MIA approval. I expect that it will take additional time finalize the MAA. Management has given no guidance on when it will file the MAA. As an out and out guess, I am estimating a filing by early June or possibly sooner. I have no meaningful information underlying this guess. It just stems from an appreciation of how complex the process is and how methodical NWBO has been in other document preparations.

How fast will the MHRA and FDA move? Given the MHRA's commitment to accelerating the approval process for breakthrough medicines for life threatening diseases and the expediting of the MIA for Sawston, I would hope for an expedited approval process in the UK. As an out and out guess, I think that approval by year end is possible. The timeline for FDA approval likely will take longer as they have less familiarity with DCVax-L. However, the FDA and MHRA have a collegial relationship and the actions of MHRA could favorably affect the FDA's approach to the BLA.

The Manufacturing Process for DCVax-L Is Incredibly Complex

I will only give a very superficial overview of the manufacturing process for DCVax-L. I would urge you to go to the appendix of this report for a more in-depth discussion.

Let me provide some perspective. Industry drug development has gone through three broad evolutionary stages with products first based on organic molecules, then intricate proteins such as antibodies and quite recently living cells. In terms of manufacturing complexity, proteins was an order of magnitude harder than organic molecules and living cells are several orders of magnitude more difficult than proteins (especially personalized living cells as used in DCVax-L, which vary greatly from patient to patient). Why? Because with living cells, the manufacturing process is actually the product. Even the slightest changes in how the cells are biologically manipulated and how they are grown, differentiated and processed in cultures can completely alter the product and render it worthless.

The manufacturing process for DCVax-L starts with a blood draw process called leukapheresis in which white blood cells are obtained from the blood. These contain a mixture of monocytes, lymphocytes, granulocytes and other white blood cells. These are shipped to the Sawston facility and the manufacturing process begins by separating out the monocytes.

NWBO must then mirrors in a laboratory environment (*ex vivo*) what goes on in the body (*in vivo*) when the adaptive immune system is activated to attack and destroy cancer cells. In vivo, monocytes go through a series of cell differentiations before becoming mature dendritic cells which can activate the immune system to create effector and helper T-cells educated to specifically kill tumor cells. This is a complex process involving several cell divisions in the body with each relying on intricate signals to the cell from other components of the immune system that control its differentiation.

The NWBO *ex vivo* manufacturing likewise induces a series of cell differentiations. At some point in this process, tumor antigens that are obtained from surgical removal of tumor cells from a patient are introduced in the process. Remember that DCVax-L is an autologous therapy only intended for the patient from whom the monocytes and tumor cells were derived. The end point of the manufacturing process is an immature dendritic cell that displays antigens that are specific to the patient's tumor. It is these cells that are the final product that is injected back into the patient where they migrate to lymph nodes, mature and present the tumor antigens that activate effector and helper T-cells to launch an attack on the patient's tumor.

The MIA Allows for Global Delivery of DCVax-L

NWBO states that its license is the culmination of more than three years work, including development of the Sawston facility, the teams of specialized personnel, the Standard Operating Procedures (SOPs) and systems, well over 1,650 regulatory documents, and a successful operating history under the initial manufacturing licenses previously obtained to produce cell therapies in the Sawston facility for clinical trials and compassionate use. All of this work was carried out by Advent BioServices under contract with NWBO.

Under this commercial manufacturing license, cell therapy products manufactured in the Sawston facility may be exported globally. Products (e.g., immune cells obtained through leukapheresis) may also be imported into the U.K. for production or release of cell therapy products under the facility's licenses. This is critically important as it allows NWBO to supply global demand from the Sawston facility.

It is simply amazing what tiny NWBO has accomplished as was well stated by Dr. Mike Scott, President of Advent BioServices. "It is always challenging to be one of the trailblazers. The field of personalized cell-based immunotherapy is rapidly evolving and we are collectively navigating our way through the regulatory landscape. We are therefore thrilled that the extensive preparatory work undertaken by our skilled and dedicated team has met the extremely high standards set for this commercial level of manufacturing license."

Appendix for Those Who Want More Information

So Just What is a Dendritic Cell?

Dendritic cells differentiate from monocytes, a phagocytic (cell eating) type of white blood cell. Monocytes leave the bone marrow and circulate through the blood. Depending on chemokine signals, they further differentiate into macrophages and immature dendritic cells. Both of these cell types also phagocytose (engulf and then digest) foreign substances such as cellular debris, infectious microbes and abnormal, damaged cells like cancer (which is what we are interested in). Both also play a role in activating the adaptive immune system, but dendritic cells are more specialized and play a much more important role. They are referred to as the professional antigen presenting cell and are considered the starting engine of any immune response.

Immature dendritic cells circulate through the blood to take up residence in tissue at potential sites where they may encounter cancer cells displaying antigens. They are present in the blood, tissues in the inner lining of the nose, lungs, stomach and intestines. These immature dendritic cells are geared for antigen capture after which they migrate through tissues following a chemokine gradient into the lymphatic system and ultimately into lymph nodes where they develop into mature dendritic cells.

Cancer cells are mutations of healthy human cells which carry abnormal molecules on their surface that do not occur or occur infrequently on normal cells. These are called antigens and when recognized as foreign, can trigger an immune response that seeks to destroy them. Cancer cells are ingested by immature dendritic cells which process digested antigen fragments and present them on their surface though MHC peptide complexes to other cells of the immune system. A killer T cell can become sensitized to an antigen by first encountering it on the MHC class I molecules on the surface of the dendritic cell. This recognition of the antigen present on the MHC class I peptide complex is generally not enough to activate killer T cells and turn them into cancer cell killers. They need the support of helper T cells. Helper T cells recognize a different collection of peptides displayed as MHC class II molecules. When helper T cells come in contact with these MHC class II molecules containing antigens, they become activated and secrete cytokines that promote the expansion and maturation of killer T cells targeted at a specific antigen(s) on a cancer cell's surface and B cells that produce antigen specific antibodies.

DCVax-L is Based on Living Cells Which Means that the Manufacturing Process is the Product

In the case of cancer, the natural immune response may not be sufficient to contain or eliminate the cancer. The goal of dendritic cell cancer vaccines is to emulate and bolster the adaptive immune response in the hope that this will allow the immune system to regain its efficacy. In effect, drug developers are trying to replicate the biology that in nature stems from the immature dendritic cell capturing antigens, migrating to the lymph nodes and differentiating into a mature dendritic cell that displays that antigen to T cells passing in the lymph. In nature, this is an incredibly complex process and perhaps no less so in the production of a dendritic cell cancer vaccine.

With living cell therapies like dendritic cell-based cancer vaccines, the manufacturing process largely determines the ultimate

characteristics of the product. The processes used to grow the cells and alter them can lead to end products which may have the same general approach and therapeutic goal, but whose efficacy can be quite different. The manufacturing starts with leukapheresis in which a tube extracts blood from one arm and runs it through a machine that separates out white blood cells and then returns the blood, which now contains primarily red blood cells and plasma, through a tube in the other arm. Over a period of a few hours, the machine can extract a considerable number of white blood cells which are then shipped to the manufacturer.

The leukapheresis product contains monocytes, lymphocytes, granulocytes and other white blood cells. The manufacturer must then separate the monocytes and culture them to obtain immature dendritic cells. The cells are spun in a process that separates the different cellular components into gradient layers based on their density; one of these layers contains the concentrated lymphocytes and monocytes. NWBO places the cells containing monocytes on a plastic dish to which the monocytes selectively adhere. They then wash away the other cells. The remaining cells are mostly monocytes. The mixture containing monocytes is given nutrients to keep them alive and cytokines that stimulate their differentiation into immature dendritic cells. Mechanical factors such as rocking the culture are also used.

The next important step is to expose immature dendritic cells to induce them to capture antigens that characterize a patient's tumor. Northwest Biotherapeutics DCVax-L uses a tumor lysate to obtain antigens for its vaccine. When the surgeon removes the tumor, a small piece is sent to the pathology laboratory for analysis. The remaining tumor is washed with saline and placed in a premixed tube containing enzymes. It is then ground up into small pieces, placed in a container and shipped to NWBO by courier.

At some point in the manufacturing process (the timing is a manufacturing art), the immature dendritic cells are exposed to lysed tumor tissue. They ingest the tissue mirroring the natural process in the body. The resultant cells are frozen at cryogenic temperatures to be later injected back into the body at various points in time; there is considerable art in this freezing process. They can be kept for three years of more so that this results in the production of numerous doses of DCVax-L that can be given at multiple time points. At the time of treatment, these cells are thawed and returned to the patient. As with the natural process, these cells circulate through the lymph system to lymph nodes where they become mature dendritic cells which trigger as immune response as just described. Like dendritic cells produced naturally, they stimulate an adaptive immune response.

More Precise and Broader Targeting of Neoantigens is the Key Aspect of DCVax-L

This therapy is patient specific in that dendritic cells are derived from the patient's monocytes and the tumor antigens specific to that patient's tumor. Proponents of this approach point out that no two cancers are the same. New proteins called neoantigens form on cancer cells when certain mutations occur in tumor DNA. Recognizing and targeting neoantigens plays a central role in helping the body launch an effective immune response against cancer cells. The number and type of antigens may change over time. This could mean that if a particular drug is developed specifically to target a prespecified antigen may not be effective if mutations have occurred. Over time the antigens specific to the tumor in its initial phase may not be present later. The excitement of the DCVax-L approach is that is based on antigens that are present at time of surgery.

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