QLT INC. – VISUDYNE® AND BEYOND

by

Joel Naor
Bachelor of Science (Technion Israel Institute of Technology, 1987)
Doctor of Medicine (Technion Israel Institute of Technology, 1993)
Master of Science in Epidemiology (University of Toronto, 2001)

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Name: **Joel Naor**

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Supervisory Committee:

Prof. Edward Bukszar Jr. , BA, MBA, PHD
Associate Professor
Faculty of Business

Jill Shepherd, BSC, DIC, MBA, PHD
Assistant Professor
Faculty of Business

Date Approved: December 14, 2004

SIMON FRASER UNIVERSITY

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ABSTRACT

QLTI's ocular franchise, comprised of Visudyne® for wet AMD, is the focus this paper. In addition to being QLTI's only commercial product, Visudyne® related activities constitute a major component of QLTI's overall operations. To this extent, issues identified are indicative of challenges facing QLT as a whole.

Imminent entry threat of competing products underscores dependence of QLTI's ocular franchise on a single product, which enjoys exclusivity, and whose control of marketing rights was relinquished to a partner. For the overall company, it highlights underutilized asset base and weakening competencies as a biotech.

Visudyne® must be differentiated. Its lifespan can be optimized by influencing the emerging market for treatment of neovascular conditions of the back the eye towards combination therapy. Cash can be used for licensing in order to secure a revenue stream and raising brand awareness. Ultimately, QLTI must rejuvenate its discovery core to secure its position as a biotech.

DEDICATION

To

Gal, my partner;

Aviva and Moshe, my parents;

and Michael, my brother.

ACKNOWLEDGEMENTS

I wish to thank Prof. Ed Bukszar, for making himself available to me at odd times and places, and for his insight, which was instrumental to the content to this work.

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1 OVERVIEW OF THE FIRM, BUSINESS BEING ANALYZED, DEVELOPMENT PROCESS, PRODUCT, AND MARKET

This paper presents a strategic analysis of the ocular business of QLT Inc. (Nasdaq: QLTI). The ocular franchise of QLTI is comprised of Visudyne® for the treatment of wet-AMD. Visudyne® is QLTI's only commercial product. Moreover, Visudyne® related activities constitute a major component of QLTI's overall operations. Therefore, where applicable, the paper will be related to QLTI as a whole.

1.1 QLT Inc.

QLTI is a global biopharmaceutical company. It is engaged in the development and commercialization of innovative therapies to treat eye disease, cancer, and niche areas for which treatments can be marketed by a specialty sales force. QLTI is a pioneer in the field of photodynamic therapy, a field of medicine that uses photosensitizers (light-activated drugs) in the treatment of disease. Established in 1981, QLTI became public in 1986. It is headquartered in Vancouver, Canada, and employs about 300 professionals in the fields of science, research, business, and technology.

To date, QLTI has commercialized two products, Photofrin® (porfimer sodium) and Visudyne® (verteporfin). Photofrin®, the world's first approved photodynamic therapy agent, was developed and commercialized by QLTI for use as either an early-stage potentially curative cancer treatment or a palliative cancer therapy for more advanced cases. QLTI received a number of worldwide approvals for Photofrin® for various cancerous conditions. On June 8, 2000, shortly after the launch of Visudyne®, QLTI sold the worldwide rights to Photofrin to Axcan Pharma for all indications except ophthalmology, restenosis, and certain immune disorders.

Choosing to focus on its more promising product Visudyne®, QLTI noted that Axcan's experience in the gastroenterology market puts the company in a good position to capitalize on additional opportunities for Photofrin, especially in treatment of Barrett's esophagus.

Visudyne®, QLTI's commercial product, was launched in April 2000. It is a photosensitizer used to treat choroidal neovascularization (CNV) in patients with the wet form of age-related macular degeneration (AMD), the leading cause of severe vision loss in people over the age of 50 in North America and Europe, as well as other less common ocular conditions.

QLT is striving to expand its pipeline by in-house development as well as evaluation of in-licensing and acquisition opportunities. Importantly, on June 14, 2004, QLTI announced the acquisition of Atrix Laboratories Inc., ("Atrix") diversifying its revenue base and product portfolio with Eligard® for prostate cancer. QLTI's vision is to be among the top ten biotechnonology companies worldwide vis-a-vis market capitalization by 2010.

1.2 QLT's Ocular Business

QLTI's ocular business is managed by a designated project team. The members of the team represent the different functions that are pertinent to the development of the product. Specifically, the group includes representatives of the following functions: project management, clinical development, preclinical development, regulatory affairs, manufacturing, and marketing.

The primary mandate of the team is to maximize the potential of Visudyne®. The team formulates strategies and makes recommendations to QLTI's executive committee. Approved strategies are implemented by the individual functions represented at the team. For example, a recommendation by the team to make a change to the manufacturing process in order to extend the shelf life of the product is brought to the executive committee. When and if the

recommendation is approved, the implementation would be led by the manufacturing representative in the project team acting within his or her function.

On February 6, 1995, QLTI entered into an agreement with Novartis Ophthalmics (NVO), the eye health unit of Novartis AG (Nasdaq: NVS), to pursue worldwide joint development and commercialization of PDT products, including Visudyne®. Under the terms of that agreement, QLTI and NVO co-develop Visudyne® and share the associated costs. QLTI is responsible for manufacturing and product supply and NVO is responsible for sales, marketing, and distribution. The profits realized on revenues from product sales after deductions for manufacturing and marketing costs are shared equally. This agreement resulted in the formation of a joint Visudyne® project team, which is comprised of the QLTI's ocular project team and their counterparts from NVO.

1.3 Drug Development Process

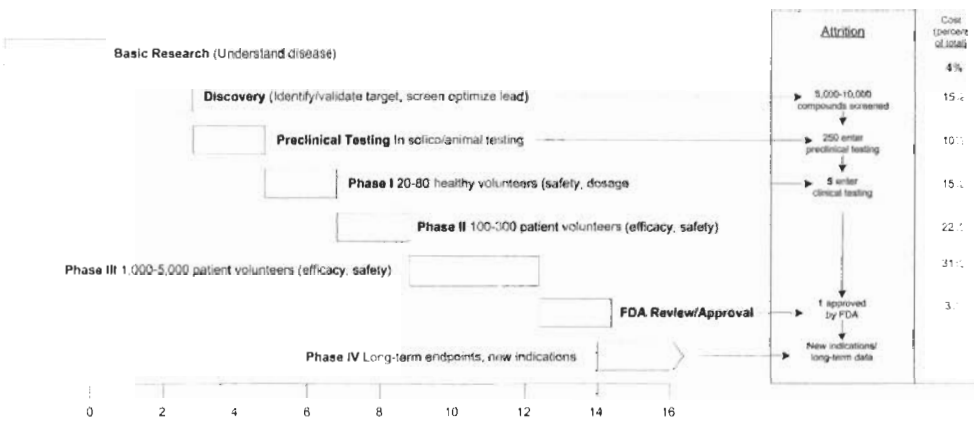
QLTI is engaged in drug development. The goal of the drug development process is to identify new chemical entities (NCE) and convert them into safe and effective therapies that will provide value to patients. Prior to marketing a drug, pharmaceutical companies are required to demonstrate that the drug is safe, effective in treating diseases for which it is indicated, and can be manufactured in a clean and reproducible way.

The typical stages of drug development, attrition rate, associated timelines, and proportional cost, are outlined in Figure 1-1 Biopharma Research Stages. The NCE is identified, formulated, and progressively tested in the laboratory, animal models, and humans. Human trials progressively establish the pharmacologic profile (distribution, metabolism, excretion, and toxicity), safety, and efficacy of the NCE. In parallel, manufacturing processes are developed and a suitable drug product is formulated.

The cost of development stages increases progressively, peaking with the pivotal human trials. Overall, the cost associated with the whole process is in the excess of US$ 500MM.[1] The development process is a lengthy one, and may take up to 15 years before an NCE gets regulatory approved. The number of compounds goes down dramatically and progressively over the development process. Eventually, few out of thousands of screened compounds will be approved for marketing and be made available to the public.

A marketing approval is not the end of the process. The marketing company is required to maintain a constant watch for adverse events and report them to the regulatory authorities. Often, additional life-cycle programs are undertaken, in order to add new indication or improve existing formulations for the drug.

Figure 1-1 Biopharma Research Stages



(Based on Simon and Kotler, 2003)

[1] Simon, Francoise and Kotler, Philip. 2003 *Building Global Biobtands: Taking Biotechnology to Market.* New York: Free Press, p. 93.

1.4 Visudyne®

1.4.1 Development Stage

As of yet, Visudyne® is QLTI's only commercial product; however, this is about to change once its merger with Atrix takes effect. In April 2000 the Food and Drug Administration approved Visudyne® (verteporfin for injection) for the treatment of patients with the wet form of AMD. Subsequently, approval for marketing of Visudyne was granted in over 70 countries including the United States, Canada, Japan, Australia, New Zealand, and those of the European Union. Since the time of the original approval development efforts were concentrated primarily at adding approvals for existing indications and obtaining approval for new indications.

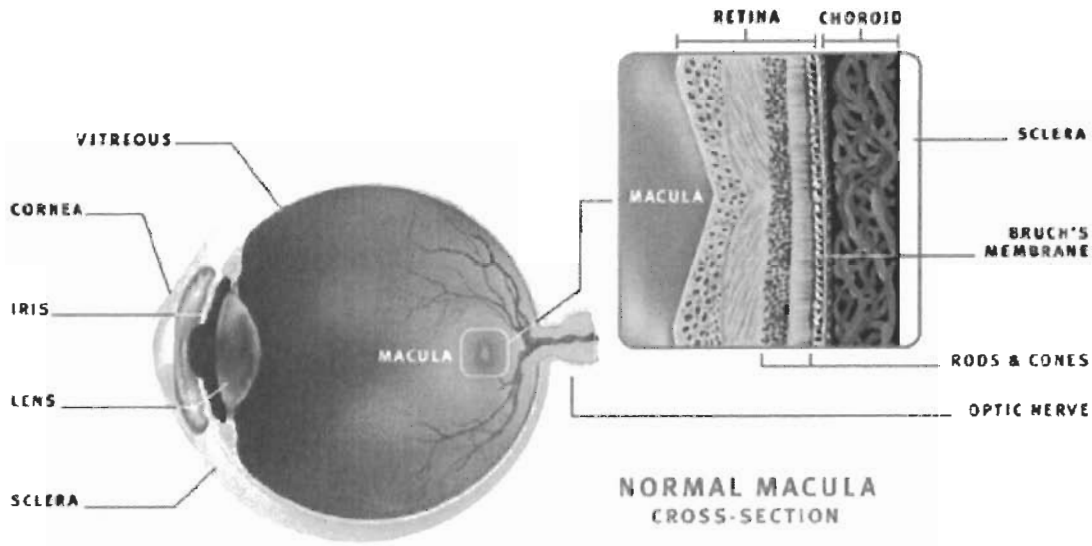
1.4.2 Wet Age Related Macular Degeneration (AMD)

AMD is the leading cause of legal blindness in Americans over the age of 65. The estimated prevalence of AMD in Americans 75 years of age or older is 7.1%. While the exact etiology of AMD is not well understood, it is thought to be a multi-factorial disease. In addition to age, several other risk factors are associated with AMD. These include family history of AMD, smoking, and light eye color. Recent findings also suggest that low dietary intake of antioxidants may predispose people to AMD.

In AMD, damage is caused to the central part of the retina called the macula (see Figure 1.2). The macula is the part of the retina used for reading and seeing fine detail. Damage to the macula leads to vision loss. There are two basic types of AMD: dry and wet. Dry AMD is the most common type, accounting for 85% of all cases. In dry AMD, central vision deterioration results from the accumulation of acellular debris, called drusen, within Bruch's membrane. Bruch's membrane, as shown in Figure 1, is the layer between the outer edge of the retina and the choroid. Wet AMD accounts for 15% of cases but is responsible for approximately 90% of the

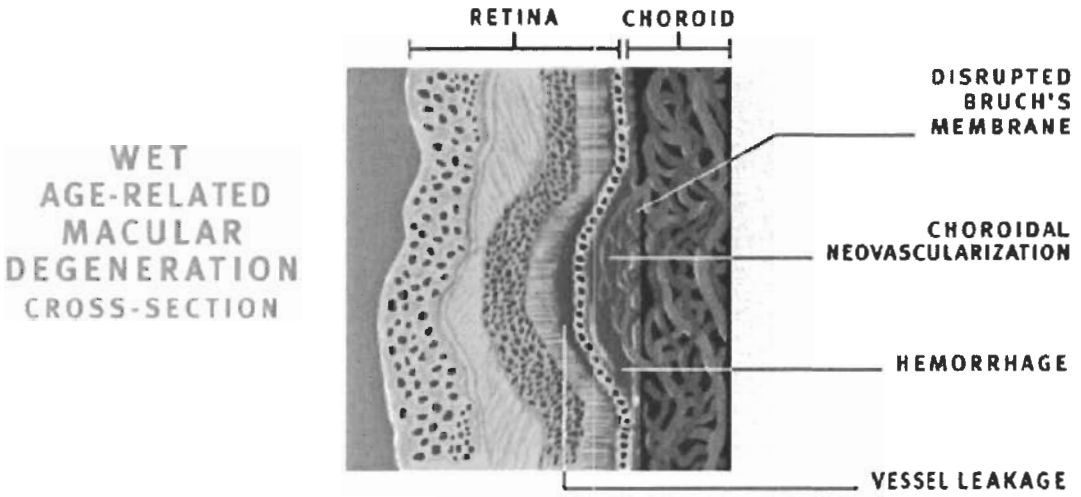
vision loss associated with the disease. In wet AMD (see Figure 1.3), breaks in Bruch's membrane allow vessels from the choroid to grow, leak, and bleed into the subretinal space; this is termed choroidal neovascularization (CNV). Although the progression of the disease varies by patient, the majority of patients with wet AMD become legally blind in the affected eye within approximately two years following the onset of the disease.

Figure 1-2 Anatomy of a Healthy Eye and a Cross-Section of the Back of the Eye



(Based on Eyetech Pharmaceuticals Inc. Form 10K, 2003)

Figure 1-3 Detailed Cross-Section of the Back of the Eye as Affected by Wet AMD



(Based on Eyetech Pharmaceuticals Inc. Form 10K, 2003)

Patients suspected of having wet AMD generally undergo Fluorescein Angiography ("FA"). This test helps identify and characterize the blood vessels in the eye. It serves 3 key functions:

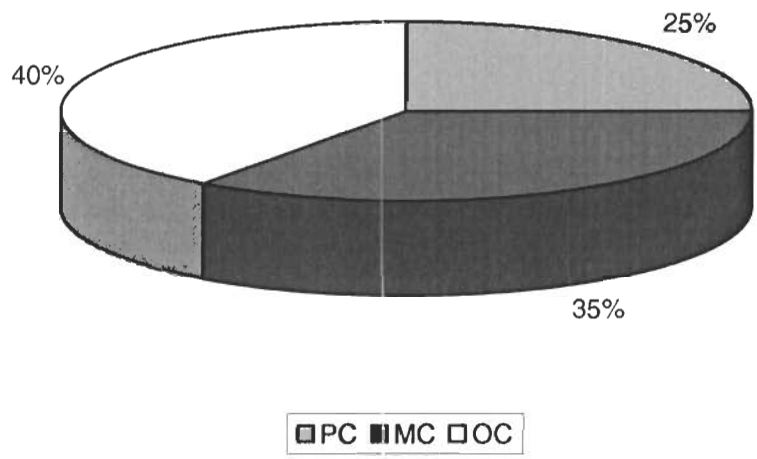
1. To differentiate between patients with the dry form of the disease and the wet form, by establishing the presence of CNV.

2. To characterize the position of the CNV in relation to the fovea (the center of the macula) by one of three locations: subfoveal, juxtafoveal and extrafoveal. Subfoveal, as the name implies, is CNV that lies directly below the fovea. Juxtafoveal and extrafoveal CNV lie progressively further away from the fovea (but still within the macula).

3. To distinguish between two components of lesions for patients who have wet AMD: classic and occult. In pure classic CNV, the choriocapillaris plexuses that are involved can be seen distinctly. In pure occult lesions, the location of the offending vessels responsible for the leakage is not recognizable. Many CNV lesions are a combination of both occult and classic with a portion showing a defined site of leakage and another portion being obscured. CNV lesions are characterized according to the ratio between the classic and occult lesion components as outlined below:

    - Predominantly Classic (PC) - classic component comprises at least 50% of the lesion.
    - Minimally Classic (MC) - classic component comprises less than 50% of the lesion.
    - Occult with no Classic (OC) - no classic component, only occult.

Figure 1-4 Estimated Breakdown of CNV due to AMD by Lesion Types[2]



[2] QLTI 2003 Annual Report

There is no definitive treatment for dry AMD. For some patients with wet AMD, laser photocoagulation has been shown to help reduce the rate of vision loss. Specifically, laser photocoagulation has been shown to decrease vision loss by 50% in juxtafoveal and extrafoveal CNV. However, for subfoveal CNV, laser treatment has been shown to have only marginal benefit, mainly in patients with classic CNV. Laser photocoagulation by itself destroys the retina overlying of the area of application. When applied away from the foveal center (i.e., juxtafoveal or extrafoveal), the effect of the laser itself on vision is variable, but when applied to the foveal center, as in cases of subfoveal CNV, the laser is almost assured to destroy some central vision. In addition, subfoveal CNV recurs approximately 50% of the time after "successful" laser therapy.

1.4.3 Ocular Photodynamic Therapy (OPT) with Visudyne®

Photodynamic Therapy (PDT) is a minimally invasive medical procedure that utilizes photosensitizers (light-activated drugs) to treat a range of diseases associated with rapidly growing tissue (such as the formation of solid tumors or abnormal blood vessels). PDT is a two-step process. First, the photosensitizer is administered to the patient by an intravenous infusion or other means, depending on the condition being treated. While circulating in the bloodstream, the photosensitizer attaches itself to molecules called lipoproteins. Because rapidly proliferating cells may require greater amounts of lipoproteins, the photosensitizer may accumulate more quickly and in higher concentrations in these cells than it does in normal cells. Second, a pre-calculated dose of non-thermal light is delivered at a particular wavelength to the target site to interact with the photosensitizer. The photosensitizer traps energy from the light and causes oxygen found in cells to convert to highly energized form called "singlet oxygen" which causes cell death by disrupting normal cellular functions. Since the photosensitizer and light have no effect unless combined, PDT is a relatively selective treatment that minimizes damage to normal surrounding tissue.

Ocular Photodynamic Therapy (OPT) for the treatment of CNV involves the intravenous injection of a photosensitive drug, verteporfin. A laser, which emits light only at verteporfin's absorption peak of 689 nm, is then directed into the eye. It is thought that the excitation of verteporfin generates singlet oxygen and other reactive intermediates that result in temporary closure of leaking blood vessels. Since the laser is non-thermal it does not produce a heat effect on the retina and thus causes no damage to the retinal tissue. Verteporfin therapy is neither a cure nor a preventative for CNV in AMD; it is meant to slow the progression of the disease. Indeed, its effect is generally not permanent. The closure of leaking blood vessels caused by OPT is often temporary. These vessels may re-open, requiring additional OPT treatments.

1.4.4 Penetration Factors

The main factors affecting Visudyne®'s penetration rates in the wet AMD market are outlined below:

1.4.4.1 Availability of Alternative Treatments

Laser photocoagulation is considered an acceptable treatment for juxtafoveal and extrafoveal CNV but only marginally beneficial for patients with subfoveal CNV. The majority of CNV lesions are subfoveal.

1.4.4.2 Perceived Drug Efficacy

CNV is characterized by the ratio between the classic and occult lesion components as outlined above. Visudyne's® efficacy profile is considered related to the CNV characteristics.[3]

[3] Effect of lesion size, visual acuity, and lesion composition on visual acuity change with and without verteporfin therapy for choroidal neovascularization secondary to age-related macular degeneration: TAP and VIP report no. 1, Blinder KJ, Am J Ophthalmol. 2003 Sep;136(3):407-18.

While its efficacy for PC lesions and for lesions with smaller size is established, its efficacy for MC and OC lesions is still debated.

1.4.4.3 Regulatory Approval and Off-Label Use

Regulatory approval for Visudyne® is not uniform across the world. Whereas it is widely accepted that Visudyne® is effective for the treatment PC lesions, its activity for other types of lesions is debated. Consequently, while regulatory approval was granted for PC lesions worldwide, approval for MC and OC lesions was withheld in some parts of the world until further evidence of efficacy becomes available.

Regulatory approval for a drug grants a company the right to market it. Approval is granted for one or more indications. Indication is the disease condition for which the approval was granted for, and is specified in the package's insert that accompanies the drug. A company can actively promote a drug only for an approved indication. Once a prescription drug is approved for a particular indication, it becomes available to patients and care providers. Typically, physicians prescribe a drug according the indication for which it was approved for marketing; however, they are not limited to doing so by law. When convinced that the drug is beneficial for a condition different than indicated, a physician may prescribe the drug for off-label use. Visudyne® can be and is prescribed for non-approved indications; specifically, small MC and OC lesions in the U.S.

1.4.4.4 Reimbursement

For high-priced drugs, reimbursement is a significant barrier to usage. Typically drugs are reimbursed only for approved indications; however, this is not always the case. Importantly, in the US Visudyne® is reimbursed by Medicare (the Federal health insurance program for people 65 years of age or older) for small MC and OC lesions.

Table 1-1 Visudyne®'s Approval Reimbursement Profile

Region / *Lesion Type*	US	EU	Japan
PC	√	√	√
OC	Reimbursement for small lesions	√	√
MC	Reimbursement for small lesions		√

1.4.5 Differentiation and Pricing

To date, Visudyne® is the only approved pharmacologic treatment for wet AMD. It is a relatively selective treatment compared to laser photocoagulation, which is only marginally effective for the treatment of subfoveal CNV lesions due to AMD. Thanks to its superior efficacy and excellent safety profile, it was quickly endorsed as the treatment of choice for PC and small MC and OC lesions.[4] Its usage seems to be primarily restricted by reimbursement considerations and not by efficacy concerns. Visudyne® was priced at US$ 1000 -1500 per treatment. Typically, multiple treatments are necessary during the first year.

The absence of alternative treatments precluded a need for a differentiation strategy and must have simplified pricing decisions. Alas, competition looming in the horizon may force QLTI to address these issues in the near future.

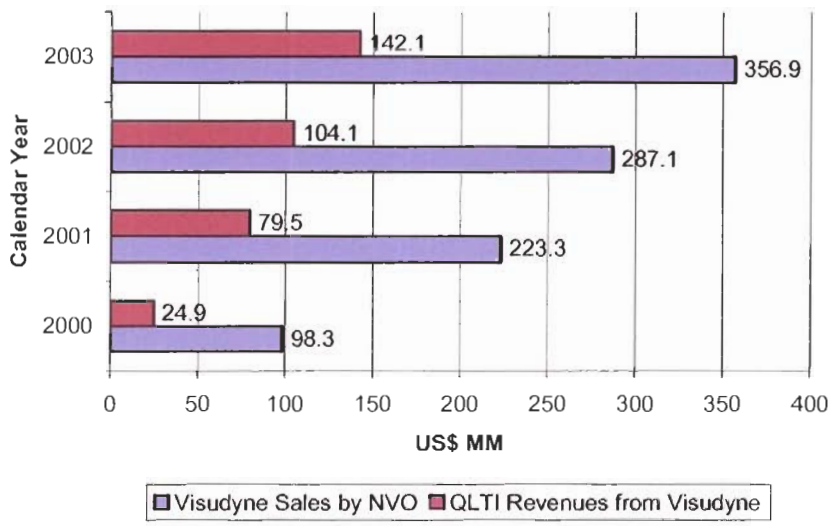
1.4.6 Revenues from Visudyne®[5]

For all practical purposes, revenues from Visudyne® constitute the sole source of revenues for QLTI. For example, in 2003, revenues from Visudyne® totalled US$ 142MM

[4] American Academy of Ophthalmology. Preferred Practic Patterns. Age-related macular degeneration, 2003. Available at: http://www.aao.org/aao/education/library/ppp/upload/Age-Related-Macular-Degeneration.pdf. Accessed December 9th, 2003.

compared to US$ 5MM from other sources. Sales and associated revenues increased steadily between the years 2000 and 2003 (Figure 1-5 Global Visudyne® Sales and Associated QLTI's Revenues from Visudyne®). Specifically, growth rates in sales were 29% and 24% for 2002 and 2003 respectively. During 2004, sales totalled US$ 101.1MM, US$ 109.3MM and, US$ 114MM, for Q1, Q2, and Q3, respectively. This represented a growth of 23.2%, 22.6%, and 27.0% over the same periods in 2003. QLTI forecasts the sales range for 2004 to be US$ 435-$455 MM, which represents top-line growth of 22% to 27% over 2003.

Figure 1-5 Global Visudyne® Sales and Associated QLTI's Revenues from Visudyne®



Visudyne® sales in the US constituted approximately 63%, 59%, and 51%, of total Visudyne® sales during the years 2001, 2002, and 2003, respectively. During 2004, US sales constituted 45%, 48%, and 50%, for Q1, Q2, and Q3, respectively. Table 1-2 Growth in Visudyne's Sales over the Same Period the Previous Year presents the growth in US sales compared to the rest of the world. Since 2002 Visudyne®'s sales have been growing faster in the rest of the world compared to the US. In its 2003 annual report, QLTI estimated Visudyne®'s

[5] QLT Inc. Financial News. Available at:

penetration in the US market to be 70% of the PC AMD market. Penetration in the EU for the same lesions was estimated to be 40-50%.

Table 1-2 Growth in Visudyne's Sales over the Same Period the Previous Year

	2002	2003	Q1 2004	Q2 2004	Q3 2004
US	20.4%	7.46%	NA	15.00%	22.00%
EU	42.47%	48.57%	NA	30.45%	32.33%

1.5 Overview of Competing Products

By addressing an unmet need, Visudyne® has become one of the most successful launched ophthalmology products. Its success has raised the interest of other biopharmaceutical companies in wet AMD. As this paper is being written, companies are releasing results of clinical trials, which will reshape the competitive landscape.

The most significant competition that Visudyne® is facing, both in terms of urgency and probability of success, is from a class of compounds termed Anti-Angiogenics (AA) or agents that inhibit the growth of abnormal blood vessels. Eyetech Pharmaceuticals, Inc. (Nasdaq: EYET), in partnership with Pfizer Inc. (Nasdaq: PFE), is developing an Anti-VEGF Aptamer, Macugen™ (pegaptanib sodium). Based on positive results from its Phase II/III pivotal clinical trials for the treatment of wet AMD, EYET had filed a New Drug Application with the FDA. Macugen™ can become available in the US as early as the first quarter of 2005. Although it does not seem that Macugen™ is more effective than Visudyne® for the treatment of PC CNV it is

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http://www.qltinc.com/Qltinc/main/mainpages.cfm?InternetPageID=104.

nevertheless likely that Macugen™ will have a more favourable label, which will include all lesion types without lesion size limitation.

Similar to Eyetech Pharmaceuticals Inc., Genentech Inc. (Nasdaq: DNA) is developing Lucentis™ (ranibizumab) - an antibody fragment to VEGF. DNA is currently conducting Phase III pivotal trials for the treatment of wet AMD. Although Lucentis™ is not expected to be approved until the last quarter of 2006, based on the similarity of its mechanism of action with Macugen™, it has a high probability of success. NVO, the eye health unit of Novartis AG, entered into an agreement with DNA, which will grant it with marketing and development rights of Lucentis™ outside North America for indications related to diseases of the eye. As mentioned earlier, NVO is responsible for worldwide sales, marketing, and distribution of Visudyne®.

Reetane® (Anecortave Acetate) is a product with a mechanism of action that is non VEGF related. It is an angiostatic steroid developed by Alcon Inc. (Nasdaq: ACL). Reetane's® was the most advanced of all Visudyne's® competitor's vis-a-vis its development stage. However, in October 2004, its timelines for development were set back significantly when it failed to meet the primary endpoint in a pivotal trial.[6] It is thought that entry to the market of drugs that compete with Visudyne® would have a dual effect. On the one hand, they will expand the market by further increasing awareness and penetration, while on the other hand they are likely to take away from Visudyne's® market share.

[6] Oct 13, 2004. News Release - Alcon Announces Anecortave Acetate Clinical Results. http://invest.alconinc.com/ireye/ir_site.zhtml?ticker=ACL&script=410&layout=6&item_id=630541

1.6 Beyond wet AMD - The Market for Pharmacological Treatment of Neovascular Conditions of the Back of the Eye

Visudyne® is a treatment for wet AMD only. However, AA, the new agents that are being developed to treat wet AMD by QLTI competitors, have the potential to address other ocular conditions with an underlying pathology of neovascularization.

Neovascularization is defined as proliferation of blood vessels in tissue not normally containing them. The newly formed vessels typically exert a harmful effect on the surrounding tissue. The retina and choroid are two tissue layers that coat the back of the eye (Figure 1). Their integrity is essential for normal vision. Two major disease conditions that are characterized by neovascularization of the choroid and retina are AMD, which affects the former, and Diabetic Retinopathy (DR), a complication of the systemic disease Diabetes, which affects the latter.[7] These conditions are two of the leading causes of age-related vision impairment and blindness in the developed world. Their prevalence will increase as the population ages and the incidences of diabetes continue to rise.

AMD and DR are grouped together because they share a few features. First, a pathological process - drugs which target neovascularization may be effective for both conditions; second, both conditions are cared for by a subset of the ophthalmic community who had special training in retinal disease, creating synergies in R&D and marketing and sales. Indeed, science and business common sense had influenced the biopahrmaceutical companies that are active in the field of retinal and choroidal neovascular conditions, to test agents for the two conditions. In addition to AMD, Visudyne® was tested for the treatment of Diabetic Macular Edema (DME), a

[7] Pathologic myopia and presumed ocular histoplasmosis syndrome are two additional conditions associated with neovascularization of the choroid for which Visudyne® is indicated. However, due to their low incidence, their impact on the Visudyne® business is insignificant.

complication of DR which results in loss of central vision. However, it was found to be effective only in the former[8]. Macugen™ too is being tested for DME as well as wet AMD.[9]

AMD and DME, represent an unmet medical need. As mentioned, Visudyne® is approved only for the PC subtype of wet AMD in the United States, and in the European Union - only for the PC and OC subtypes. Hence, approved therapy is indicated only for approximately 25% of the United States patients and 65% of the European patients. Furthermore, the current treatment options, including laser photocoagulation and Visudyne®, offer only partial solutions. For example, wet AMD patients treated with Visudyne® continue to lose vision, albeit at a slower pace. DME is a complication of DR, which similarly to wet AMD, results in loss of central vision. There is no approved treatment for DME in either the United States or the European Union. The current therapies for the treatment of DME are thermal laser and steroid treatment administered on an off-label basis. The former treatment does not result in an improvement of vision in most patients. Furthermore, it results in localized damage to portions of the retina. The latter treatment does not have an established efficacy profile, and is associated with cataract formation and induction of elevated intra-ocular pressure.

AMD is the leading cause of severe vision loss and blindness in patients over the age of 65 in the developed world. Currently, as many as 15MM individuals in the United States and 30MM worldwide have some form of AMD. In the United States more than 1.6MM experience the advanced form of AMD (wet AMD). Age is the main risk factor. The prevalence of AMD increases from 18% among people 70-74 years of age to 47% among people 85 years and older. Hence, the prevalence is expected to increase significantly as the population ages. Approximately 200,000 and 500,000 cases of Wet AMD are diagnosed annually in the United States and

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[8] Verteporfin (Visudyne) in the treatment of Diabetic Macular Edema (VIDME): 3 month results of a phase I/II placebo controlled trial. Elman M., ASRS, August 2004.
[9] Form 10-K Eyetech Pharmaceutical Inc - EYET, filed: March 24, 2004 (period: December 31, 2003) p. 15 (hereinafter: "Eyetech 10-K").

worldwide, respectively. The majority of patients become legally blind in the affected eye approximately two years following disease onset.

DR is the leading cause of blindness in working age adults and a leading cause of vision loss in diabetics. There are approximately 18MM diabetics in the United States. DR affects more than 7MM Americans and over 20MM people worldwide. Importantly, DME affects more than 750,000 people in the United States alone, and over 2.5 million worldwide. Obesity is the major risk factor for developing diabetes and its complications. As the population becomes more obese and ages, the prevalence of diabetes and DR will escalate.

1.7 Conclusion

This chapter introduced the reader to QLTI's ocular franchise. The ocular business operates within the framework of the biopharmaceutical industry's drug development process. The franchise consists of a single product, Visudyne®, for the treatment primarily one disease condition, wet AMD. This product enjoys exclusivity in the marketplace. The primary penetration factors for Visudyne® are its perceived efficacy, which is not uniform across all subtypes of wet AMD, and regulatory and reimbursement status, which vary geographically. Visudyne® sales are the primary source of revenue for QLTI. Several competing products are at late stages of development and may enter the marketplace within the next five years. These products have the potential to address ocular complications of diabetes in addition to wet AMD. The concepts introduced in this chapter provide the necessary background to understand the industry in which QLTI's ocular business competes which is the subject matter of the next chapter.

2 INDUSTRY ANALYSIS

This chapter will present the framework for understanding the industry in which QLTI operates. Industry scope will be defined, QLTI's value chain outlined, and the germane competitors analysed. Structural analysis of the industry will be used as a tool to establish the industry attractiveness and determinants of relative competitive position.

2.1 Industry Characterization

2.1.1 Scope

In its broadest definition, the industry that QLTI belongs to is the global healthcare industry. In the U.S., with a market cap of US$ 2238B, healthcare is the fourth largest economy sector among 12. The healthcare industry can be further subdivided into the following sub-industries: major drugs, biotechnology and drugs, medical equipment and supplies, and healthcare facilities. With a market cap of US$ 1225.1 and 569.5 B, respectively, the major drugs and biotechnology constitute together nearly 80% of the U.S. healthcare sector. These two industries also produce products that are closely related to each other. Traditionally, vertically integrated pharmaceutical firms (firms that belong to the major drugs industry) were involved in developing drugs from small usually organic molecules, which were purified from living organisms, especially plants; whereas the biotechs (firms that belong to the biotechnology and drugs industry) exploited newer technologies in order to develop large molecules, like nucleic acids and proteins. However, the distinction between the two is not based only on scientific attributes. Financial elements must play a role, given that on the average market cap in the biotech industry

is US$ 219MM with 132 employees compared to a market cap of US$ 61.47B with 63.2K employees in the vertically integrated pharmaceutical firms.

Importantly, both industries produce drugs, which compete in the ocular therapeutic space, and more specifically address neovascular conditions of the back of the eye (hereinafter: "NCBE"). Therefore, in the next section, which sketches the industry value chain, the scope of the industry is the biopharmaceutical industry as a whole encompassing the major drugs and the biotechnology and drugs industries. However, when key competitors are outlined, the scope is narrowed to companies with current or pending business in the market of NCBE.

2.1.2 Value Chain

This section will outline the key components of the value chain of the biopharmaceutical industry from drug discovery through development, manufacturing, and eventually marketing and sales, and will address the pertinent differences between biotechs and vertically integrated pharmaceutical firms.

2.1.2.1 Discovery

Discovery is the process of formulating or identifying a chemical entity and experimenting with it in the laboratory and up to the level of animal models. The distinguishing feature of the biotech industry is the ability to identify and produce *customized* biological agents, which would influence disease processes, whereas the vertically integrated pharmaceutical firms typically employed screening methods of many agents in a trial and error process. Many biotechs are small non-profitable companies experimenting with an idea, using equity that they have raised in an attempt to enter the industry. Hence, by design, biotechs are assuming more risk than the vertically integrated pharmaceutical firms and thereby being more innovative. Survival of a biotech typically depends on possession of expert scientific capabilities related to the particular

area in which it operates. Ideally, a vertically integrated pharmaceutical firm will possess similar core competencies; however, it can compensate for the lack thereof.

2.1.2.2 Development

Development refers to the process that starts after Proof of Concept (POC) had been established, typically in an animal model of the disease. It is comprised of lengthy human trials performed in multiple sites around the world and according to guidelines put forth by regulatory agencies. The process includes establishing dose and method of administration, and ultimately proof of efficacy and safety. The desired outcome of the development process is approval to commercialize the product in a particular jurisdiction.

Occasionally, the operational tasks related to drug development are contracted out to Contract Research Organizations (CRO). However, for most biopharmaceuticals, development is a core competency. Ergo, even the leanest company would possess scientific expertise in development as it relates to its drug, as well as act as the communicator of the trial results to the regulatory agencies. On average, biotech and vertically integrated pharmaceutical firms do not differ much in their competencies in development.

2.1.2.3 Manufacturing

Manufacturing of drugs for commercial purposes is subject to Good Manufacturing Practices (GMP), mandated by regulatory agencies. Economies of scale and scope can play a role, depending on the particular agents and associated processes. Typically, the smaller the company and its portfolio, the less likely it is to engage in manufacturing. Smaller biotechs would contract out manufacturing to Manufacturing Contract Organizations (MCO). Core competency in manufacturing can provide a competitive advantage but it is not considered a key success factor.

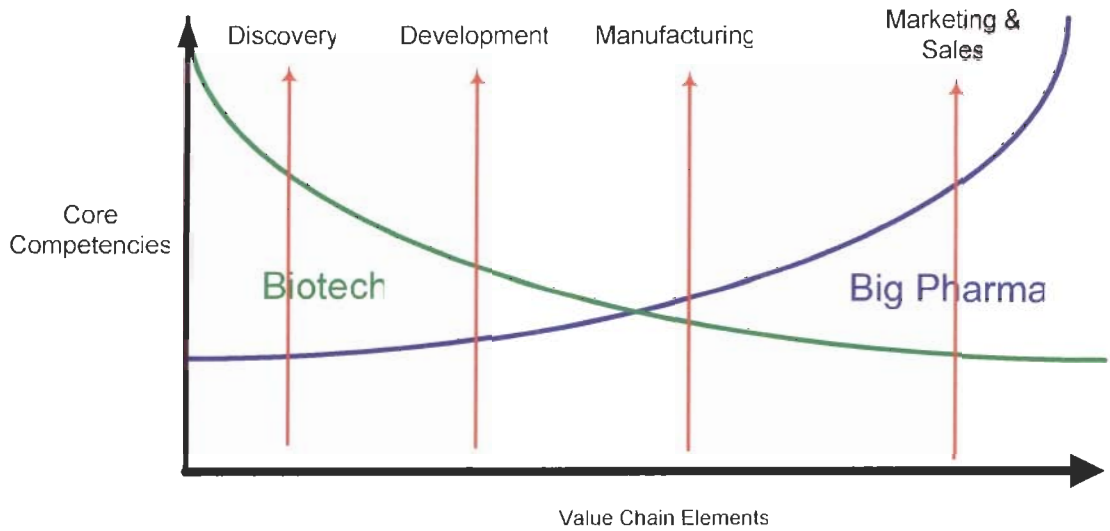
2.1.2.4 Marketing and Sales

Marketing and sales is the component of the biopharmaceutical value chain that truly reflects the global nature of the industry. More often than not, the intention is to market drugs worldwide. Only a handful of companies have enough sales representatives enabling them to reach out to physicians across the world; one such company is Pfizer Inc., with a global sales force of 30,000. Like manufacturing, marketing and sales is also subject to economies of scale and scope. This is the distinguishing feature of the vertically integrated pharmaceutical firms and where their core competencies reside. The only way to overcome this barrier for small biotech is through a strategic alliance with a larger company.

2.1.2.5 Summary

The biopharmaceutical industry is grossly made up of two categories of companies (industry segments) whose core competencies are skewed towards opposite ends of the industry's value chain (see Figure 2-1 Biopharmaceutical Industry Value Chain). By way of generalization, biotechs have a stronger footprint on the discovery side while vertically integrated pharmaceutical firms possess a dominant footprint in marketing and sales. It is interesting to note that these two competencies are typically hard to substitute for by outsourcing as opposed to development and manufacturing, the components in the middle of the value chain.

Figure 2-1 Biopharmaceutical Industry Value Chain



The prevailing wisdom is that the biotech/pharma symbiosis is such that pharma needs the biotech's innovation, and biotech needs pharma's scale. Thus, biotech is more discovery-focused while vertically integrated pharmaceutical firms possess global marketing and sales clout. While generally speaking this is still the case, the border between the two industries is rapidly blurring. And although global sales of vertically integrated pharmaceutical firms still dwarf biotechnology sales, the latter has reached a stage where its top-tier firms are full-fledged biopharmaceuticals.

2.1.3 Key Competitors

The ocular business of QLTI faces diverse competition: biotech and vertically integrated pharmaceutical firms, incumbents and new entrants, single companies and alliances, as well as competition from its own partner to the development and commercialization of Visudyne®. This section will outline the germane competitors.

Table 2-1 German Competitors to QLTI

	Biotech	Pharma
Incumbents	AGN	NVO ACL
New Entrant	EYET DNA	PFE

*similar colours represent alliances

2.1.3.1 The Eyetech / Pfizer Alliance

Eyetech Pharmaceuticals Inc. (Nasdaq: EYET) is a biotechnology company which commenced operations in April 2000 and positioned itself as specializing in the treatment of diseases of the eye. Markedly, its management team includes recognized scientists experts in ophthalmology and vision research. Its most advanced product is Macugen™, which it is developing for the treatment of wet AMD and DME. Macugen™ will potentially be EYET's first commercial product. EYET has yet to show profit.

Pfizer Inc. (Nasdaq: PFE) acquired Pharmacia on April 16, 2003 for an estimated US$ 56B, solidifying its position as the world's largest pharmaceutical company. Pursuant to the deal, PFE gained presence in three additional clinical areas, one of which is ophthalmology. Xalatan®, a first line therapy for glaucoma, is legacy Pharmacia. During the acquisition year Xalatan® had become the first ophthalmic treatment to achieve 1 billion US$ in annual sales.

In December 2002 EYET and PFE entered into an agreement to develop and commercialize Macugen™ for the prevention and treatment of eye disease.[10] Pursuant to the terms of the agreement, PFE will make initial payments of US$ 100MM, with the potential for an additional US$ 195MM in milestone payments based on worldwide regulatory submission and approvals. EYET also has the potential to receive up to additional US$ 450MM in milestone

[10] Eyetech 10-k page 15

payments, which are contingent upon the successful commercialization of Macugen™ and based on attainment of agreed-upon sales levels. PFE will also fund the majority of the ongoing development costs for both the AMD and DME indications. Under the terms of the agreement EYET will co-promote Macugen™ in the United States. EYET had granted PFE the exclusive right to develop and commercialize Macugen™ outside the United States pursuant to a royalty-bearing license. EYET is also entitled to participate in selling PFE's product, Xalatan®, for the treatment of glaucoma in the United States.

The terms of this agreement provide EYET with visibility in the ophthalmic marketplace and partial control over marketing and sales of Macugen™. It provides EYET with a platform to become a brand in the ophthalmic market place. The agreement between QLTI and NVO denied the former this opportunity.

PFE, the other partner to the alliance, seems to have made a significant commitment to the field of ophthalmology. Not only had it acquired Pharmacia with its blockbuster drug Xalatan®, it had also entered a deal with EYET, which potentially grants it with a foothold in a rapidly expanding market for NCBE.

Given the terms of the agreement, it seems that both companies are expecting Macugen™ to generate significant revenues. There is already evidence that that PFE is leveraging its marketing muscle to justify its investment. PFE sponsored the American Academy of Ophthalmology meeting in October 2004 in the amount of US$ 1.65MM, second only to Alcon Inc. by insignificant US$ 5,000.[11]

[11] American Academy of Ophthalmology, 2004, Final Program Book

2.1.3.2 The Genentech / NVO Alliance

Genentech Inc. (Nasdaq: DNA) can be considered the founder of the biotechnology industry and one of the world's leading biotechnology companies. Like EYET and PFE, DNA is a new entrant to the ophthalmic arena. DNA leverages its scientific know-how in the field of vascular biology, to enter the field of NCBE with Lucenetis™.

Novartis Ophthalmics (NVO), formerly part of CIBA Vision, and now operating under the Pharmaceutical Division of parent company Novartis AG (Nasdaq: NVS) as its eye health unit, is an incumbent in the field of NCBE, being QLTI's partner to Visudyne®. To QLTI's chagrin, NVO brings into the alliance with DNA considerable intellectual capital, and wealth of experience in development and marketing and sales.

In June 2003, DNA and NVO announced that they have entered into an agreement under which NVO will receive an exclusive license to develop and market Lucentis™ outside of North America for indications related to diseases of the eye. Under the terms of the agreement, DNA and NVO will share certain global development costs. DNA will receive an upfront fee, payments for achievement of clinical development milestones, and royalties on net sales of Lucenetis™ outside North America. DNA will retain marketing rights for Lucenetis™ in North America (United States, Canada and Mexico).

This agreement positions NVO as a key player in the field of NCBE. In addition to being intricately involved in the development and marketing of Visudyne®, the only approved pharmacologic treatment for wet AMD, it will now have access to an anti-angiogenic, a compound that belongs to the second most promising class of agents to treat NCBE. It also puts an interesting spin on its collaboration with QLT, as NVO may find itself developing and marketing two potentially competing products outside North America.

2.1.3.3 Alcon Inc.

With sales in 2003 of US$ 3.4 B, Alcon Inc.'s (Nasdaq: ACL) global sales represent 20% of the ophthalmic pharmaceutical market, 47% of the ophthalmic surgical market and 19% of the ophthalmic consumer market, making ACL the largest and most profitable specialized ophthalmic company worldwide.[12] ACL was established as "Alcon Prescription Laboratory" in 1945. By 1970, its sales had reached US$ 25MM, and by 1977 it became part of Nestlé, the world's largest food company, headquartered in Switzerland.

In an attempt to enter the market for NCBE and maintain its leadership position in the ophthalmic area, ACL has been developing Reetane® (Anecortave Acetate), an angiostatic steroid, for the treatment of wet AMD. Reetane's® development stage was the most advanced of all Visudyne's® competitor's. However, in October 2004, results of its comparative study to PDT were released, disclosing that it failed to meet the primary non-inferiority endpoint.[13] This represents a significant setback to the clinical development of this product, pushing its tentative approval dates beyond these of Macugen™ and Lucenetis™.

2.1.3.4 Allergan Inc.

Allergan, Inc. (Nasdaq: AGN), is a global specialty pharmaceutical company that develops and commercializes innovative products for the eye care, neuromodulator, skin care and other specialty markets. In July 2002 AGN spun off its ophthalmic device business, creating a new publicly traded company American Medical Optics Inc. (NYSE: AVO), presumably to shed off its lower margin device business.[14]

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[12] Alcon Overview - http://invest.alconinc.com/ireye/ir_site.zhtml?ticker=ACL&script=2100
[13] Oct 13, 2004. News Release - Alcon Announces Anecortave Acetate Clinical Results. http://invest.alconinc.com/ireye/ir_site.zhtml?ticker=ACL&script=410&layout=6&item_id=630541
[14] Allergan Inc. *Form 10-K* 2001

While AGN is not developing a product to directly compete with Visudyne® for the treatment of wet AMD, it is actively pursuing opportunities to develop drugs for the treatment of NCBE. Indeed, on November 20, 2003, AGN completed the acquisition of Oculex Pharmaceuticals, Inc., for US$ 223.8MMs. [15] Oculex's lead investigational product, Posurdex®, is a proprietary, biodegradable, sustained-release implant that delivers dexamethasone to the targeted disease site at the back of the eye. Phase 2 clinical trials for Posurdex® showed promising results for the treatment of macular edema, including that associated with diabetes.

2.2 Structural Analysis[16]

In this section the structural elements that shape biopharmaceutical industry in general, and the market for NCBE in particular, will be analysed.[17]

2.2.1 Rivalry Amongst Competitors

Overall the rivalry among existing competitors is low. The NCBE industry is growing. There are only a few competitors, and they offer differentiated products. High exit barriers and diversity amongst competitors act to increase competitive pressure. Below is a short explanation for each of the above mentioned factors.

2.2.1.1 Positive Market Growth

The strong and consistent increase in Visudyne® sales suggests that the market for wet AMD is not saturated. Moreover, there are two major forces that will increase the pool of

[15] Allergan Inc *Form 10-K* 2003.
[16] Porter M E, Competitive Advantage: Creating and Sustaining Superior Performance, New York, The Free Press, 1985 pp 6
[17] Please refer to Figure 1.7 – Biopharmaceutical Industry Structure.

potential customers (or patients) with NCBE. First, the emergence of treatments is an incentive to diagnose more patients, and at an earlier stage of the disease. Since Visudyne® was approved 4 years ago diagnostic methods have improved technologically; awareness has heightened.[18] The second factor that contributes to the growing market is the shifting demographics of the population. The proportion of the elderly increases as the life span is extended. The incidence of AMD and Diabetes both increase with age. The latter is also associated with obesity, which is also on the rise. Positive market growth is a major contributor to reduction in the rivalry among existing competitors.

2.2.1.2 Differentiated Products

The proprietary drug industry relies on patented technologies. Patents protect against the introduction of similar products during the patent term. Since the industry for NCBE is relatively young the drugs are in early development stages and expiry dates of patents are far into the future. Even Visudyne®, the veteran, is protected for the remainder of the decade. Thus, coexisting products will be non-homogenous and are likely to have different attributes. For example, Visudyne® is likely to have a better safety profile when compared to Macugen™ or Lucentis™, which are administered by an injection into the eye (whereas the former is administered intravenously). Patent protection reduces rivalry and competitive pressure.

2.2.1.3 Low Concentration of Incumbents

As of yet, QLT is the only company with an approved product in the market. The number of companies with products in the clinical development stages *i.e.*, one to 10 years from launch, is less than 10. Moreover, it is likely that not all the products that are being developed will make it to the clinic. For example, Miravant Medical Technologies developed Photrex™ (rostaporfin,

[18] www.notal.com

SnET2), a compound with a mechanism of action similar to Visudyne® *i.e.*, a photosensitizer, very shortly after QLTI. However, clinical trials failed to meet the primary endpoint. The relatively small number of companies active in the space is a factor that reduces rivalry among existing competitors. Similarly, the imbalance and relative strength between the firms reduces the likelihood of confrontations and encourages formation of alliances, in order to maximize profits.

2.2.1.4 High Exit Barriers

Drug development is a highly specialized field in which intellectual capital, a specialized asset, plays a significant role. Failure to demonstrate the desired effect of the drug leaves the investor with very little value to be recovered from liquidation. Rather than exit, companies try to fully exhaust the possibility of getting a product approved. For example, Miravant Medical Technologies is raising additional funds in order to enable it to focus on completing a New Drug Application process for Photrex™.[19] It will seek regulatory approval for a subset of patients despite failure of its pivotal trials. Its probability of success is very low. Clearly, the effect of the high exit costs is to increase rivalry among existing competitors.

2.2.1.5 Diverse Competitors

The competitors in the industry for NCBE are very diverse. ACL, AGN, NVO, and QLT are incumbents. PFE, EYET, and DNA are new entrants. The latter may introduce a new set of "rules to the game" which may result in increasing rivalry. DNA is new to the field of Ophthalmology altogether. It may behave according to the codes of competition of the Oncology field to which it is used. Rivalry may intensify simply as a result of companies having difficulty reading each other's intentions.

[19] Miravant Medical Technologies. Press Release October 11 2004.

Related to the diversity are potentially different strategic stakes in the field. EYET is a biotech whose profitability depends upon a successful product in the market. Other companies like AGN or ACL may have higher tolerance by virtue of being more diversified. Any of these companies may be willing to sacrifice profitability for different reasons. Profitability may be compromised in different forms, for example, an expensive and aggressive development program. DNA is conducting an unusually high number of parallel trials with its lead product Lucentis™. One can only speculate, whether this is related to changing the "rules of the game", willingness to sacrifice profits, or another reason.

2.2.2 New Entrants

The industry for drugs to treat NCBE is characterized by low to moderate threat of entry. Entry barriers, which reduce the threat to entry, are common to the biopharmaceutical industry as a whole, and include requirements for capital, economies of scale, and regulatory requirements. Factors which influence in the opposite direction are scientific and technological progress and low branding barriers.

2.2.2.1 Capital Requirement

The need to invest large amounts of capital in risky and potentially unrecoverable lengthy research and development efforts decreases the threat of entry in the biopharmaceutical industry. For example, EYET's expenses on R&D in U.S. dollars were 22MM, 40MM, and 71MM, during 2001, 2002, 2003, respectively.[20] Drug discovery and development is characterized by increasing chances of success going hand in hand with increasing costs (See Figure 1.1). However, even in the later stages of development, success is spotty. Since only a few companies have enough reserves to sustain losses over prolonged periods, more often than not small innovative companies

[20] Eyetech 10-K 2003 page 32

end up sharing costs in the context of an alliance with a larger partner. High capital requirements have the effect of decreasing the threat to entry.

2.2.2.2 Economies of Scale

Scale economies are present in nearly every stage of the industry value chain; where they are most significant is in marketing and sales. Drugs are typically sold globally however, only a handful of organizations have the infrastructure necessary to market and sell products internationally. Furthermore, an international presence does not necessarily imply an established presence in a certain therapeutic area. For example PFE entered the therapeutic field of ophthalmology only after Pharmacia's acquisition.

The scale of the marketing and sales organizations of the giant pharmas is colossal. For the year ended December 31, 2003, the marketing and distribution costs for Visudyne® by NVO were 110 MM U.S. dollars. Small companies, which do not have an established marketing and sales infrastructure, find it risky and costly to invest in developing an infrastructure, particularly before a drug candidate is granted final approval by the regulators. Yet, by the time an approval for marketing is received, developing an infrastructure would result in delays and loss of potential revenues. Having said that, the economies of scale associate with marketing and sales have only a moderate impact on the threat to entry since once a suitable candidate is identified, a partner for an alliance can usually be found.

2.2.2.3 Regulatory Barriers

The costly R&D process is partially mandated by the regulatory authorities. Lengthy and complicated animal experiments and human trials are required in order to prove efficacy and safety of the drug prior to the granting of approval to market it. This factor reduces the threat of

entry because, in addition to the prohibitive cost, it requires significant scientific and operational expertise of the entrant. It further introduces the risk of failure due to chance alone.

An interesting situation faces a new entrant in the presence of an existing drug for a given indication. Marketing approval for the new alternative drug can be granted by one of two ways. The first and more risky is proof that the new drug is superior to the existing standard of care. Once superiority is established, the new drug is likely to become the standard of care. The second and more common route to approval constitutes a lower hurdle - the new drug is proven to be as good as the existing one. Yet, superiority of the drug with respect to a particular attribute is not established. Moreover, it is unlikely that more comparative information will ever become available. The competitors have no incentive to pursue such information since the risk is that their drug could be proven inferior. Under these circumstances, the consumer (physicians and or patients) will make a choice with less than ideal information and consequently, the relative importance of marketing increases. For example, the pivotal trials run by EYET were not designed to demonstrate superiority of Macugen™ over Visudyne® in patients with PC lesions. If and when Macugen™ is approved for treatment in patients with PC lesions, no definitive comparative information to Visudyne® will be available. Overall, this option makes entry into the market somewhat easier as well as alleviates potential competitive pressures.

2.2.2.4 Scientific / Technological Progress

Both Macugen™ and Lucenetis™ block VEGF. However, they rely on different patented processes to do so. Regeneron Pharmaceuticals has yet a third proprietary technology to achieve a similar objective; namely, a VEGF trap. The list goes on and on. Scientific and technological progress can reshape industries by nullifying barriers to entry *e.g.*, bypassing patents. It could also make existing products obsolete. For example, one of the most significant challenges facing the treatment of NCBE is drug delivery. Currently, Macugen™ and Lucenetis™ are being

delivered by way of intraocular injections, which significantly compromise the safety profile for the drug and the risk benefit ratio of using it. The first company to address this challenge in a satisfactory manner will leapfrog any industry leader. Scientific progress is a force that increases the threat of entry.

2.2.2.5 Low Branding Barriers

Health being the subject matter, once a product has established its superiority; it is quickly adopted by physicians and health insurers. The healthcare market has a low tolerance for co-existence of products of different established efficacy profiles. A well-known brand name means less in the proprietary drug market than in the generic drug market. Low branding barriers have the effect of reducing threat to entry.

2.2.3 Suppliers

Suppliers of the biopharmaceutical industry are employees, contract organizations (primarily research and manufacturing), and patients and physicians who participate in clinical trials. The industry in general is characterized by a high bargaining power of suppliers. In the particular industry for treatments of NCBE, the power of physicians and patients is balanced by the high unmet need.

2.2.3.1 Labour

The biopharmaceutical industry relies on a highly skilled and specialized work force. Industry experience is highly regarded since formalized education geared directly at drug development is rare and the process is multidisciplinary. Companies are constantly competing to attract experienced employees, turnover is high, and clusters are typical. Consequently, the bargaining power of employees is high. This translates into attractive compensations and above

average working conditions. Biopharmaceuticals are often ranked high in employee satisfaction surveys. In a new and growing market such as the market for NCBE, the bargaining power of employees is further amplified because the rate by which experts are produced lags behind the demand. QLTI is particularly vulnerable because of its location away from the biopharmaceutical clusters in (e.g., California or New Jersey). This results in a more difficult hiring process but a higher retention rate. Once attracted, an employee threshold for leaving is higher because the alternatives are associated with relocation. In general, the increased bargaining power of employees results in attractive salaries and benefits packages.

2.2.3.2 Contract Organizations

Biotechnology companies, and less often vertically integrated pharmaceutical firms, often rely on contract research organizations for provision of services. Contract Manufacturing Organization (CMO) and Contract Research Organizations (CRO) must comply with GMP and GCP (Good Clinical Practices), respectively. These are specialized companies, typically adhering to high quality standards that come at an equally high price. Projects usually are of a long-term nature with very high switching costs. For example, a pivotal clinical trial in the field of NCBE may cost as much as 20 MM U.S. dollars over a period of 3 to 4 years. Typically, a CRO that runs the trial assumes responsibility for all operational aspects of the trial, including collecting and analyzing the data. Switching a CRO in the midst of a trial is a logistical nightmare. Any delays in data collection will translate to a delayed submission to the regulators, and hence delayed sales. Indeed, when choosing a service provider for clinical trials, it is critical to ensure that it has a very low probability of going out of business during the trial's duration and that appropriate plans to address such unfortunate circumstances are in place. The combination of the above factors translates into a force that increases the bargaining power of the contract organizations.

2.2.3.3 Patients Physicians

Drug approval is dependent on the conduct of clinical trials. A trial involves one or more clinical sites. A site is a clinic where a physician, the Principal Investigator (PI), recruits subjects from his patient pool to participate in the study. The availability of physicians to participate in and patients to volunteer for, a trial is essential to the development process. Clearly, due to the possibility of ethical dilemmas, the incentives that the biopharmaceutical company may provide are heavily regulated. The effect of the regulation is to somewhat decrease the inherently high bargaining power of physicians and patients.

The availability of alternative treatments to the condition under investigation is an independent factor. The unsatisfactory treatments for NCBE increase the motivation of patients and physicians to participate in the trials. Thus, in this specific therapeutic area, unmet need tempers the typically high bargaining power of patients and physician as suppliers of clinical trials.

Physicians' bargaining power is nevertheless likely to increase by the sheer fact that the pool of retina specialists that can conduct clinical trials in the NCBE area is rather limited, and the demand to recruit these physicians for concurrent trials is increasing.

2.2.4 Customers

The strongest force operating in this dimension is high value added. To the consumer of healthcare, a drug can provide the highest value possible - his or her own survival. Clearly, this force would act to nullify the bargaining power of the consumer. However, many other opposing factors balance this force; specifically, high buyer concentration and volume, increasing health care costs, low information asymmetry, and low switching costs. The end result is a moderate bargaining power of customers.

2.2.4.1 High Value Added and Unmet Need

Health, the desired outcome of using the offered products, has a very high value to individuals and society at large. Hence, the quality of the product is important to buyers, making them less price sensitive and willing to pay more for differentiated products. Moreover, at the presence of an unmet need, willingness to pay premiums is high. This force reduces the bargaining power of customers.

A second factor which contributes to the high unmet need is the unsatisfactory effectiveness of current treatments for wet AMD and DR. Visudyne® and Macugen™ do not stop nor reverse the loss of vision in the majority of treated patients. Their effect is limited to decreasing the rate of vision loss. Clearly, drugs that have a more potent effect or act by a different mechanism, potentially at an earlier stage of the disease, would benefit patients compared to existing agents.

2.2.4.2 High Buyer Concentration and Volume

Decisions on pricing of a drug and its reimbursement are made by governments and third party payers. The concentration and volume of buyers change across countries and continents. For example, in Canada medical insurance is available to all citizens. Pricing decisions for drugs are negotiated with the company at a federal level and reimbursement decisions are made at a provincial level. However, even in countries like the US, where buyers are generally more fragmented, buyers are high volume insurers who possess significant negotiating power.

The buyer concentration and volume may depend on the particular condition that the drug is addressing. AMD is a disease of elderly people. In the United States, Medicare is a national health insurance company that covers nearly 40MM patients over the age of 65. When Medicare

announced its decision to reimburse for the usage of Visudyne® for wet AMD patients with OC and MC lesions, it had an immediate impact on the price if QLT stock.

2.2.4.3 Increasing Health Care Costs

As technology advances more therapeutic modalities become available resulting in increased health care costs. The industry's products represent an increasing proportion of the buyers' costs. Thus buyers are very sensitive to price. The relative scarcity of resources is translated to pressure on drug companies to reduce prices. For example, it is increasingly common for regulators and reimbursement agencies to consider pharmaco-economic data, in addition to the traditional safety and efficacy information, in their decision-making processes.

2.2.4.4 Low Information Asymmetry

Drug regulations mandate disclosure of all relevant information to patients and physicians. Accompanying every drug is a package insert that outlines the attributes of the drug, contraindications, and side effects. Regulations also minimize the degree of disinformation. Physicians and patients alike have high incentives to remain informed. Physicians need to provide the best care to their patients and are especially exposed to liability for malpractice. For these reasons physicians and patients occasionally try to influence the regulators to approve or remove drugs from the market. Availability of information puts the buyer in a better position to assess the added value of the product.

2.2.4.5 Low Switching Costs

Only in a minority of patients must stay with a specific drug throughout the treatment of their condition. Occasionally, significant upfront investment made by third party payers, physicians, or patients, creates switching costs. For example, physicians invested in lasers in

order to administer PDT. Yet, switching cost can be a factor only when the efficacy and safety profile of the alternative drug is similar. Assuming better efficacy and safety, third party payers, physicians, and patients cannot use the incurring of additional expenses as a justification not to switch to the new drug.

2.2.5 Substitutes

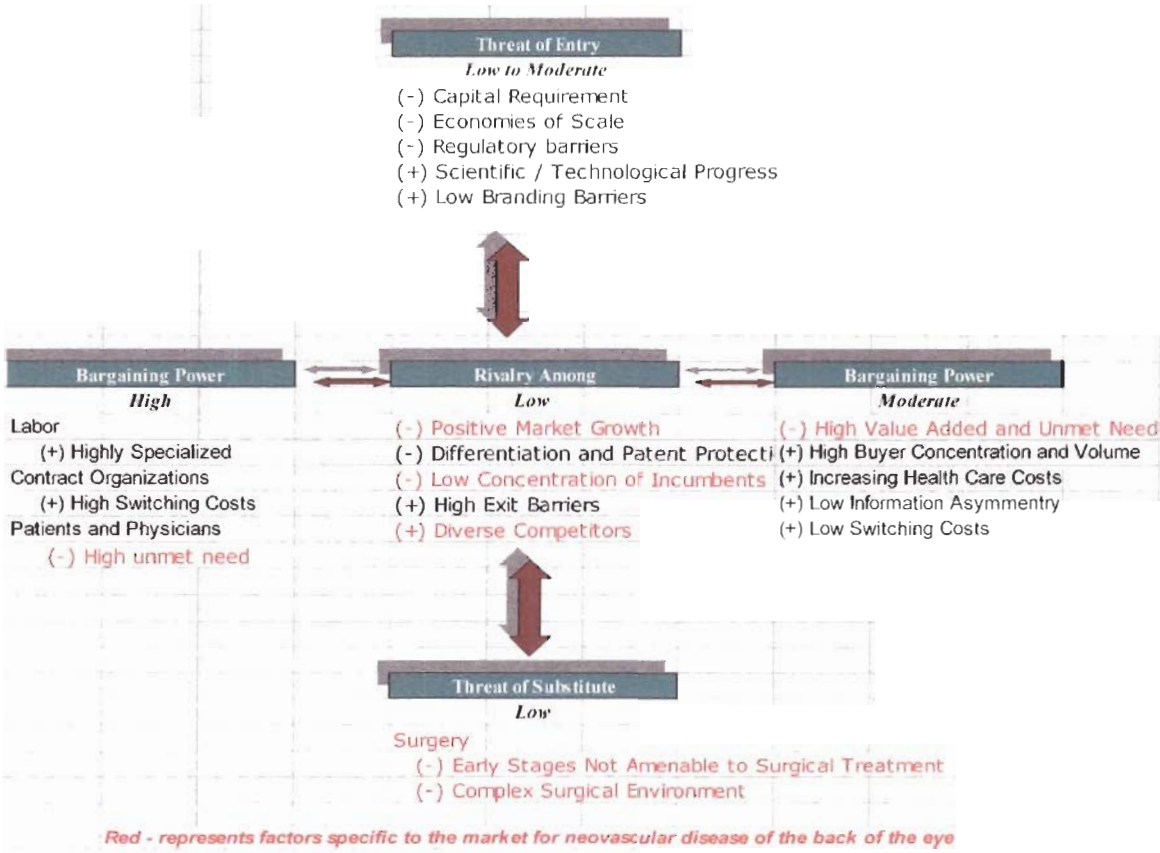
Surgical treatment can be considered a substitute to pharmacological treatments for NCBE; it nevertheless represents a low threat.

Early stages of AMD and DR are not amenable to surgical solution. Surgical treatment of later stages, namely wet AMD and Proliferative D.R. is complicated by the following factor. The eye, and specifically the retina, is an intricate surgical environment. This translates to a low success rate and a high complications rate. The recently released results of the Submacular Surgery Trial (SST) failed to show a benefit for patients with wet AMD.[21] Pan-retinal laser photocoagulation for the treatment of Proliferative D.R. has a very high success rate in terms of sparing the central visual field of the affected patient. However, it does so by sacrificing the peripheral field altogether, leaving much room for improvement. The natural history of AMD and DR, being slowly progressing conditions, makes them less amenable to surgical treatment as the acute manifestations tend to recur. Thus, the threat of surgical treatment as a substitute to pharmacologic treatment for AMD and DR is decreased by the nature of the diseases and their location.

[21] AAO 2004, Retina Subspecialty Day, Late Breaking Developments

2.3 Attractiveness

Figure 2-2 Biopharmaceutical Industry Structure



Based on Porter, 1979.

The attractiveness of the industry is determined by its profitability, which is the sum of the 5 factors in the structural analysis. In an industry with high rivalry, high threat of entry, high bargaining power of suppliers and buyers, and high threat of substitutes, it is hard to retain the value created. The industry of NCBE is part of the wider biopharmaceutical industry. A new entrant must overcome difficulties in the form of capital requirements, lack of economies of scale, and regulatory barriers resulting in significant advantages to incumbents. However, once in the industry, companies typically enjoy high profits. These profits are facilitated primarily by patent

protection and differentiation, factors that reduces the rivalry among the existing competitors. A second major contributor to high profitability is the high added value provided by drugs in general. This factor reduces the price sensitivity and the bargaining power of buyers. Among other things, the high profits enable the industry to cope with the high bargaining power of suppliers that is typical to this industry.

Elements specific to the industry of NCBE provide additional incentives to take on the daunting task of entering the field. The most significant factor is a positive market growth, fuelled by increased diagnosis, and the growing incidence of the disease conditions. Market growth relaxes rivalry among competitors, as they must channel resources to cope with growth. It also tempts new entrants with prospects of high profits.

Overall, as part of a wider phenomenon common to the biopharmaceutical industry, the narrower industry for NCBE is more attractive to incumbents than to new entrants. Compared to rest of the spectrum of the biopharmaceutical industry this specific industry is particularly attractive due to its attributes. DNA is an example of an incumbent in the biopharmaceutical industry attempting entry to this narrower industry. Noticing the potential, it was in a position to leverage scientific expertise and capital.

2.4 Key Success Factors

Key success factors stem from the industry analysis. Incumbents have a competitive advantage in the biopharmaceutical industry; they have better access to capital. Capital is used to fund the lengthy research and development process. Without capital, companies have to surrender control (or some of the value that they create) to providers of the funds. The second important element that incumbents generally possess is an experience curve; experience translates into increased efficiency in critical elements like dealing with regulators, conducting research,

manufacturing, and marketing, ultimately resulting in a greater yield. Scale is yet another key success factor usually possessed by incumbents. The advantages of scale are in manufacturing and most obviously in marketing, where sales forces are worldwide and networks with buyers are established. A readily available standing infrastructure saves time and money in conducting multinational clinical trials and provides expert advice on regulatory matters. Scale can also translate to a balanced portfolio. A company with a balanced portfolio has multiple drugs, at different stages of development. A balanced portfolio enables a firm to assume risk and absorb losses. Scale can also provide leverage when dealing with suppliers. Contract organizations will be less sensitive to price in expectation of future business. Employees can enjoy a more stable environment and be less exposed to fluctuations related to failure of success of individual products.

Highly differentiated products are another key success factor in the biopharmaceutical industry. Research and development capabilities are the means to that end. Although scale and capital can be used to promote innovation, they are not a prerequisite. The key to innovation is skilled people experienced in the relevant science and capable of taking advantages of technological progress. In the industry for treatments of NCBE, QLT and NVO have accumulated significant 'know-how'. EYET seems to have a core of experts in the field, and DNA is applying expertise from a related field and a track record in innovation.

2.5 Conclusion

The objectives of the external analysis were to analyse the structure of the industry in which QLTI ocular business operates, to establish its attractiveness, and identify the factors necessary to maintain a competitive position. The implications for QLTI are thus outlined.

The industry for NCBE is attractive when compared to other areas of the biopharmaceutical industry because of its growth prospects. QLTI managed to overcome the significant barriers to entry to this industry with its innovative product Visudyne®. It stands to reason that it is in its interest to leverage its position as an incumbent in the market for NCBE to further its growth. In order to remain an incumbent it must sustain and develop key success factors so it remains in a competitive position.

The co- existence of two classes of companies, that manufacture similar products, biotech and vertically integrated pharmaceutical firms, suggest that they must have distinct functions. The value chain of the biopharmaceutical industry revealed that, generally speaking, the core competencies of the biotech and vertically integrated pharmaceutical firms are skewed towards opposite ends of the value chain: the former towards discovery, and the second toward marketing and sales. Structural analysis showed that the biopharmaceutical industry favours incumbents and that new entrants face significant entry barriers. Incumbents can be both vertically integrated pharmaceutical firms and established biotech, however new entrants to the biopharmaceutical industry are exclusively biotech. Furthermore, the key success factors typical of incumbents like capital and scale are also characteristics for the vertically integrated pharmaceutical firms, while innovation can originate in both vertically integrated pharmaceutical firms and biotech.

The conclusion is that vertically integrated pharmaceutical firms and biotech complement and feed each other. Biotechs carries risk to a degree that would be unacceptable to shareholders of vertically integrated pharmaceutical firms, whereas the latter maintain scale, which usually impedes flexibility and stands in the way of innovation. Generally speaking, the biotech sustains the industries innovation while vertically integrated pharmaceutical firms provide biotech with the means to enjoy the value provided by their innovation. In the case of new biotech, overcoming entry barriers will depend on strategic alliances. The industry for NCBE provides an

excellent example of the symbiosis between vertically integrated pharmaceutical firms and biotech, incumbents and new entrants.

The implication is that in order to maintain a competitive position in the industry, in any therapeutic space, companies must possess competencies typical of biotech or vertically integrated pharmaceutical firms. Once they establish their position as one or the other they will more often than not form an alliance to complement their competencies. QLTI entered the industry as an innovator. The next chapter will examine its current footprint and whether its competencies remained these of an innovator and continue to position it well in the face of competition.

3 INTERNAL ANALYSIS

In the previous chapter the industry, in which QLTI's ocular business competes, was characterized. In particular, the key success factors were identified. This next chapter will present an internal analysis of QLTI with special emphasis on its ocular business. The objective is to examine how well aligned are competencies, that the ocular business at QLTI can draw upon, with the ones necessary to compete in the industry.

3.1 Strategic Fit Analysis

As a proprietary drug maker, QLTI strives to make unique products, marketed under exclusive rights that are valuable to its customers. Its strategy is that of differentiation. This section will examine alignment between QLTI's capacities and the strategy it pursues.

3.1.1 Product Strategy

Photofrin® and Visudyne® are unique products with a distinct mechanism of action. QLTI is a pioneer in the field of photodynamic therapy. To date, it remains one of the few companies in the world to venture into this field. Moreover, it was the first company in the world to apply this technology to ophthalmology.

QLT's innovation record goes even further. AMD represented an unmet need and Visudyne® was the first pharmacologic treatment approved for this disease. QLTI's venture into this area triggered an interest in the market for NCBE. In fact, QLTI was joined and followed by pharmaceutical giants like NVO, DNA, and PFE, who have put in place development programs of their own. In May 2003, QLTI received the Helen Keller Prize for Innovation in Eye Care for

the development of Visudyne®. QLTI's product strategy in the ophthalmic field is very much aligned with a differentiation strategy.

3.1.2 R&D Expense[22]

During the years 2001, 2002, and 2003, QLTI's total research and development expenses were US$ 32.8, 43.9, and 42.3 MM, respectively. Its total revenues during the same time were US$ 32.4, 83.4, and 110.5 MM, respectively. The exact proportion that is spent on ocular programs is not public information. However, given size and stage of the program relative to other reported initiatives, it must be the majority. In total, R&D expenses have increased over time but decreased as proportion of revenues as the company became profitable. Clearly, the company's research and development expenses constitute a very significant proportion of its revenues. This fits well with a differentiation strategy.

Table 3-1 R&D expenses for QLTI and its Competitors during the year ending December 2003 compares QLTI to its competitors with respect to R&D expenses during the year ending December 2003. Vertically integrated pharmaceutical firms like PFE and NVS spend a smaller proportion of their revenues on R&D. ACL is a combined device/drug company, which explains its particularly low percentage spend on R&D. Notably, AGN, a bigger and established competitor, spends substantially more. EYET does not have a commercial product yet. Its revenues are from licence fees and reimbursement of development costs, both from its partner PFE.[23] In the context of its competition, QLTI's spending on R&D is on the high end of the spectrum. For the year ending December 2003, R&D costs and net income were almost identical! As a recent entrant to the industry, QLTI must rely on innovation more than vertically integrated pharmaceutical firms since it lacks the other attributes of its bigger competitors.

[22] QLT Inc. *Form 10-K* 2003 (hereinafter: "QLT 10-K").
[23] EYET 10-K

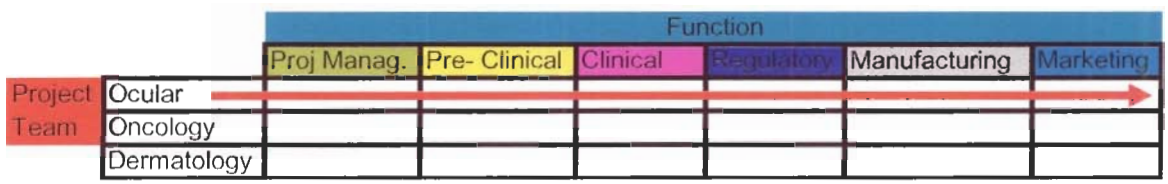
Table 3-1 R&D expenses for QLTI and its Competitors during the year ending December 2003[24]

	QLTI	EYET	AGN	DNA	ACL	NVS	PFE
Total Revenues	147	41	1771	3300	3406	24864	45188
R&D Expenses	45	71	764	722	350	3756	7131
R&D/Revenues	30.6%	173.2%	43.1%	21.9%	10.3%	15.1%	15.8%

3.1.3 Organizational Structure

To a great extent, the organizational structure at QLTI supports its differentiation strategy. QLTI operates in a matrix with project/portfolio structure *i.e.*, cross-functional project teams (see Figure 3-1 Matrix Structure at QLTI). Project members belong to the designated team (ocular, oncology, etc,) and split their time between the project and their functional responsibilities. The ocular portfolio is managed by a team comprised of representatives from project management, clinical, preclinical, regulatory, manufacturing, and marketing. This serves the purpose of developing a complex product which requires input from diverse parties. The project related tasks usually do not take the employee's whole time, with the exception of the project manager.

Figure 3-1 Matrix Structure at QLTI



The matrix form of management can be regarded as an early form of 'network' structure, which is in line with a knowledge-based industry. It focuses on project teams, bringing skilled individuals together from different parts of the organization. Individuals are accountable to both their direct supervisor and their project. It prevents duplication and confusion and fosters

[24] www.financeyahoo.com

creativity necessary to develop uniqueness. The participation of people from different backgrounds and disciplines encourages unrestrictive thinking that promotes innovation. The team is at the intersection of influences from diverse parts of the structure, and by itself influences other parts of the structure. Every participating organization or department is at the point of intersection of competing forces with each part giving particular expression to the overall system's goal.

Other structural changes at QLTI that supports its differentiation strategy were put in place in May 2003, when all research and development functions were consolidated under the Executive VP for Research and Development and Chief Medical Officer, who in turn, reports to the CEO. This included the following functions: preclinical research, clinical research, quality and regulatory affairs, and manufacturing.[25] The remaining departments, namely finance, business development, corporate communication, marketing, human resources, and project management all report directly to the CEO. This change emphasized the unity of the operational elements of the company and encouraged enhanced collaboration between them. Moreover, discovery and clinical research were united together under one VP, who reports to the Executive VP for Research and Development. This last modification reflected an understanding that R&D is at the heart of the company's success and ability to produce superior products. Silos at the R&D level hinder the probability that drugs will make it all the way through the pipeline. Products must be assessed and developed with input from the key players in all subsequent and antecedent stages of development.

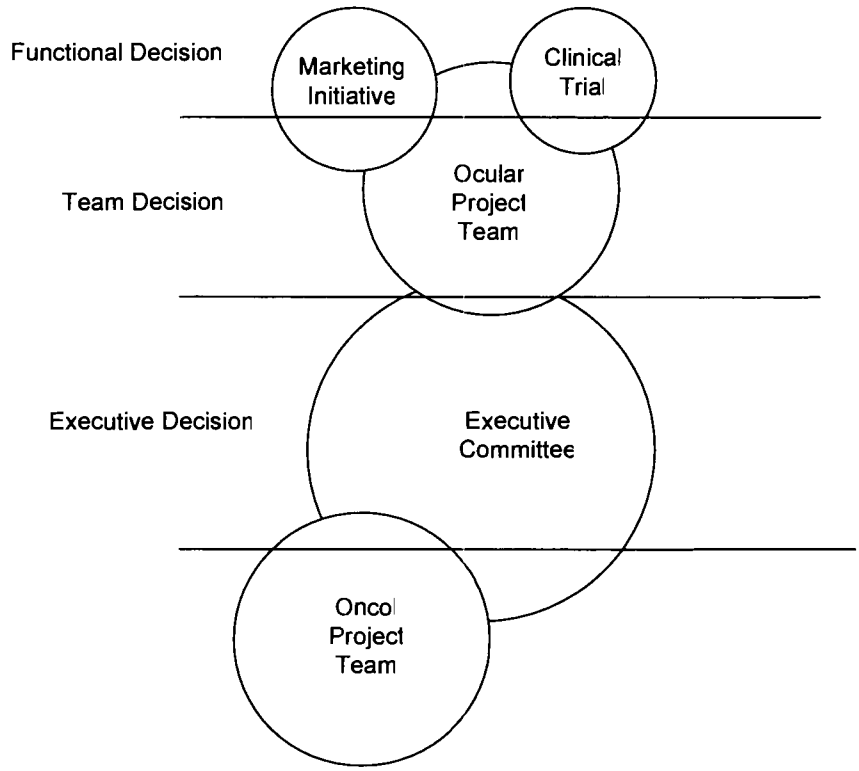
[25] QLT Inc. Press release. 20 May 2003.

3.1.4 Decision Making

The organizational structure influences the decision making process to a great extent. A decentralized matrix structure ideally cuts back the dominance of management with respect to decision making. This system tends to diminish the visibility of authority and emphasize consensus as an operating mode. Operating decisions are part of the give-and-take of specialized units struggling for a share of the system's total resources. Any element in the team has the power to freeze the dialogue of decision making. In place of a rigid hierarchy and the pressure to conform to directives from the top, the matrix management tries to substitute operating unit drive for expression within a climate of mutual respect united around fundamentals.

In QLTI, the ocular project team formulates strategies and makes the recommendation to the Executive Committee (EC) (see Figure 3-2 Circles of Decision Making at QLTI). Strategies, which were endorsed by the EC, are implemented by the individual functions. Operational decisions, regarding the implementation of the strategic decisions, are made within the functions. Changes to scope, timelines, or budget above a specified threshold, are deemed material, thus go back before the EC.

Figure 3-2 Circles of Decision Making at QLTI



Although, in theory, a bottom up approach for decision making is encouraged, in practice, this becomes more difficult. Due to functional reporting structure, the opinions that the function representatives bring to the team are often strongly influenced and reflective of the policy of the function to which they belong. In addition, several other factors stand in the way to autonomous decisions in QLTI. First, QLTI has not yet fully matured. Having grown in size from about 50 to approximately 400 employees within the last 5 years, QLTI is struggling with a legacy of a small company where all decisions were made by senior management. Second, QLTI consists of one head office with no subsidiaries, making the executive physically close to the teams that manage the projects. Third, having a modest pipeline with a single commercial product, on which current profitability is reliant, is conducive to intervention. Hence, although the structure and intention are in place to encourage autonomous decision-making aligned with a differentiation strategy, there is room for improved implementation.

3.1.5 Manufacturing

Visudyne® is currently manufactured in stages by several contract facilities located in the U.S., Canada, Europe, and Japan. QLTI has long-term supply agreements with Raylo Chemicals, Nippon Fine Chemicals of Japan, Parkedale Pharmaceuticals, Merck KGaA, Harimex Ligos BV and Sato Pharmaceuticals for manufacturing activities in the commercial production of Visudyne®. The key starting materials for the Visudyne® manufacturing process are secured by long-term supply agreements.[26]

The decision to outsource manufacturing of Visudyne® was most probably multi-factorial. Lack of required expertise in large scale staged manufacturing of a complex product, lack of economies of scale, and the need to ramp up production immediately after marketing approval was granted in order to realize revenues; all must have played a role. Manufacturing is not considered a core competency of QLTI.

Nevertheless, in order to maintain manufacturing flexibility that supports innovation and differentiation, the company is currently constructing a Pilot Manufacturing Facility (PMF) within its headquarters facility.[27] The PMF is not intended for large-scale supply. It will produce material for the discovery and development programs. The facility is expected to be operational by the end of 2004. Similarly, the company has an animal facility on site that allows independent and quick conduct of experiments involving small animals.

Manufacturing in the knowledge industry can be extended beyond the manufacturing of the physical chemical entities, to include the manufacturing of other products across the value chain. These are knowledge products manufactured by experienced employees. Employee

[26] QLT 10-k, page 8

flexibility is essential because of the high failure rate and turnover of projects across different therapeutic areas. The flexibility translates to the ability and willingness to multitask, switch projects, and, if necessary, functional hats. This is especially needed in QLTI, which is isolated from the biotechnology clusters in the US, and at a disadvantage with regards to spill over effects. The relationship between differentiation, innovation, and labour is further discussed in the next section.

3.1.6 Labour

QLTI's R&D focus dictates a need of highly educated and specialized workforce. Indeed, the R&D functions constitute more than 50% of QLTI's 400 employees. This core group is supported by expert functions like information technology, finance, and HR.

Experience and exposure at the individual employee level facilitate innovation much like an inter-disciplinary team does. Flexibility and adaptability are inherent to QLTI's workforce by virtue of its education level. QLTI policies are designed to actively promote the skills and flexibility of its workforce. QLTI emphasizes mobility of employees across related disciplines. It is not uncommon to find scientists who have migrated to different therapeutic (*e.g.,* from cancer to dermatology), or to different functions like project management or business development. Sometimes a progression could be linked to the development stage of a product. For example, a scientist who had worked on the clinical development of a product would join the medical marketing once the product had reached the commercialization stage. Furthermore, QLTI facilitates transfer and change by providing a variety of internal training courses that emphasize generic as well as specialized skills and are open to all employees.

[27] QLT 10-K, page 8

3.1.7 Culture

Schein defines culture as "a pattern of shared basic assumptions that the group learned as it solved its problems of external adaptation and internal integration, that has worked well enough to be considered valid, and therefore, to be taught to new members as the correct way to perceive, think, and feel in relation to those problems".[28] The culture of an organization is mostly tacit knowledge. Actions and procedures that are put in place attest to it. In this section an attempt is made to characterize QLTI's culture and its relationship to its differentiation strategy.

Employees believe that QLTI is a good place to work. It has been recognized as on of the Top 50 Employers in Canada,[29] and The Best Companies to Work for in BC.[30] QLTI states on the careers section of its website that it believes in balance between personal and professional goals. QLTI offers opportunities for high quality of life outside the office. It is based in Vancouver BC, one of the most beautiful cities in the world, and offers a comprehensive benefit package which includes flexible working hours. This is balanced with a challenging and rewarding working environment. Reward is partially based on personal achievement. Attainment of pre-specified personal objectives leads to increases in salary and yearly bonuses. QLTI recognizes the value of people to its business. In order to sustain a differentiation strategy, QLTI must be able to attract and retain the talented individuals who drive innovation. Recognizing that its target employees are in high demand, QLTI makes a conscious effort to provide an attractive and rewarding environment.

QLTI also makes an effort to find the right balance between personal achievements and teamwork. Teamwork is specifically recognized in order to provide a shared sense of purpose, while individual accountabilities are kept clear. Attainment of pre-specified unit and company

[28] Schein, Edgar H. 1992. Organizational Culture and Leadership. San Francisco: Jossey-Bass Publishers
[29] Report on Business Magazine (2002, 2003, 2004)
[30] BC Business Magazine 2002 and 2003

objectives factors into the yearly bonus and the employee stock option plan. This fits nicely with a differentiation strategy which relies on teams and networks to drive innovation.

QLT is an equal opportunities employer. As such it strives to ensure that decisions pertaining to employment activities, including hiring, promotion, job assignment, training and rewards, are made on the basis of qualifications, ability and performance. This promotes diversity, which is at the core of a differentiation strategy. Diversity catalyzes new ideas as well as legitimizes individual perspectives.

QLTI provides employees with ample opportunities for professional development through internal and external courses, participation in conferences, and a scholarship program. Excellence in science mandates current knowledge. This is essential to a strategy that relies on differentiation.

Finally, the business of biotechnology is about providing drugs that alleviate diseases; it is about affecting people's lives and making them better. Employees must ultimately work towards and believe in this goal. QLTI promotes this value by supporting the needs of the community through sponsorship programs. This action promotes a sense of special purpose in employees.

3.1.8 Marketing

QLTI has a collaborative agreement with NVO under which the latter is responsible for sales, marketing and distribution of Visudyne®. Nonetheless, QLTI contributes significantly to marketing strategy: primarily, by way of better familiarity with the product.

As a patented drug with no competitors as of yet, Visudyne® does not have to compete on price. It is marketed on the basis of its special attributes and in that sense, is

marketed with a pull strategy. Considerable amounts are spent on advertising and direct sales people who stimulate demand. QLTI and Visudyne® are further differentiated by pioneering, large scale, industry sponsored, clinical trials in the area of NCBE. Its trials have set the gold standard for this industry in terms of the design and quality. Its research program has produced a noteworthy amount of material for ongoing academic presentations. As well, through active participation in the trials, key opinion leaders and retinal specialists had familiarized themselves with the use of this new drug. Physicians are motivated to participate in seminars, where results of clinical studies are being presented, in order to receive Continuing Medical Education (CME) credits.

The combination of a high-priced patented drug with a pull marketing strategy is consistent with a differentiation strategy. Yet, sales representatives who are visiting the physicians' offices on a regular basis could be considered as part of a push strategy. As well, it could be viewed as having some elements of a business-to-business marketing, where the two parties are typically well informed of the product attributes and relationship plays a significant role.

3.1.9 Risk Profile

Risk is the possibility of loss. In the previous chapter, the biopharmaceutical industry was characterized as assuming high risks in expectation of high returns. The risk is inherent to the expensive and lengthy development process that has a low probability of success (see Figure 1.1). The lofty returns materialize in the form of highly differentiated end products, which create vast value to customers. Vertically integrated pharmaceutical firms that are successful in mitigating these risks are rewarded by stability. The first method is a balanced portfolio of multiple drugs at different stages of development, where many failures are more than offset by

the occasional success. The second means is gravitating towards the later activities of the industry value chain, where the risk is reduced.

Small biotech like QLTI cannot afford any of these luxuries. QLTI's limited scale allows it to concentrate only on the more risky end of the spectrum of the industry value chain. Its primary value creating activities are discovery and development. Furthermore, it cannot afford more than a few products at a time. One such product was Tariquidar. In August 1002, QLTI licensed it from Xenova Group plc ("Xenova") for the development and marketing rights in North America. Two years later, in May 12, 2003, QLTI halted both phase III trials following a recommendation by the Independent Data Safety Monitoring Committee (DSMC), which completed the unblinded review of the data, and called into question the efficacy and safety of the drug.[31]

In the next section the conservative capital structure of QLTI will be described. The conservative capital structure facilitates the risk taking which is part of the differentiation strategy.

3.1.10 Summary

QLTI's strategy within the biopharmaceutical industry is differentiation. Its footprint is skewed towards this end of the spectrum. Its product strategy relies on innovation and its R&D spending is high, especially as it relates to the ocular group. It has a decentralized matrix structure in place and encourages team decisions. However, it is struggling with growing pains and the legacy of a small company. Consequently, decision making lacks autonomy. Manufacturing is not a core competency at QLTI but flexibility enabled by small-scale capacity is a priority in order to support innovation. Labour is highly skilled and the culture provides a challenging yet comfortable environment. Marketing is not a core competency but to the extent

that it is practiced through support of NVS, it is aligned with a differentiation strategy. Finally, high risk is a part of a differentiation strategy in this industry and can best be undertaken with a conservative cap structure.

3.2 Financial analysis

QLTI belongs to the healthcare sector of the economy. Its main competitors in the market for NCBE come from two sub-industries: biotechnology and drugs and vertically integrated pharmaceutical firms. The average market caps of a company in the former and latter are US$ 145.75MM and 62.14B, respectively (see Table 3-2 Financial Data Relating to QLTI and Its Competitors). QLTI belongs to the former. At US $1.1B, its market cap is the smallest among its competitors. Of note is that 3 of its competitors, DNA, NVS and PFE, are among the top 5 market caps of their industry.

[31] QLT Inc. Annual Report 2003 page 17.

Table 3-2 Financial Data Relating to QLTI and Its Competitors[32]

	QLTI	EYET	AGN	DNA	Biotech Industry	ACL	NVS	PFE	Major Drugs Industry
Market Cap	1.1B	1.7B	10.3B	50.3B	0.145B	22.7B	117.4B	202.6B	62.14B
Employees	329	159	4,930	6,226	97	11,900	78,541	122,001	63,200
P/E (TTM)	20.8	NA	60.3	76.5	40.0	28.1	23.4	23.5	20.3
Financial Strength									
LT debt/equity ratio	0.33	0	0.57	0.06	0.39	0.46	0.09	0.12	0.34
Quick Ratio (MRQ)	28.8	8.68	2.45	2.42	3.56	0.93	1.86	1.13	1.23
Current Ratio (MRQ)	31.04	8.84	2.91	3.12	4.26	1.28	2.4	1.55	1.73
Growth (%)									
EPS (MRQ) vs Qtr. 1 Yr. Ago	25.79	NA	21.47	14.44	-10.41	27.03	15.96	51.92	19.07
EPS - 5 yrs growth rate		NA		26.9	25.45	10.18	-0.17	-15.11	1.09
Sales (MRQ) vs Qtr. 1 Yr. Ago	21.61	NA	15.23	47.2	25.65	16.46	13.64	3.91	5.64
Sales - 5 yrs growth rate		NA	6.45	25.45	25.45	9.4	-1.56	14.23	9.26
Profitability Ratios (%)									
Gross Margin (TTM)	83.14	NA	81.11	82.58	68.24	71.94	76.82	83.46	73.59
Gross Margin - 5 year Average	85.47	NA	77.3	76.98	68.05	70.49	73.82	83.53	73.56
Operating Margin (TTM)	44.04	NA	16.62	23.75	12.53	28.87	24.13	22.14	23.57
Operating Margin - 5 year Average	8.95	NA	13.44	5.16	5.83	23.94	23.09	24.95	24.31
Net Profit Margin (TTM)	31.43	NA	8.84	16.63	8.13	21.47	21	17.55	18.1
Net Profit Margin - 5 year Average	39.08	NA	8.93	-12.13	1.46	14.38	21.03	18	17.56
Management Effectiveness (%)									
Return on Assets (TTM)	8.24	NA	9.02	7.89	0.29	19.14	11.89	7.55	11.86
Return on Assets - 5 yr Average	5.34	NA	6.63	-2.77	-2.37	10.62	10.81	14.41	14.47
Return on Equity (TTM)	11.75	NA	19.9	10.45	5.34	49.53	17.09	13.46	24.13
Return on Equity - 5yr Average	5.02	NA	13.82	-3.32	2.33	35.26	14.26	31.33	31.69
Efficiency									
Revenue/Employee (TTM)	522040	NA	399351	680976	672912	320387	348850	424246	381166
Asset Turnover (TTM)	0.26	NA	1.02	0.47	0.7	0.89	0.57	0.43	0.89

MRQ -Most Recent Quarter
TTM - Trailing Twelve Months

3.2.1 Financial Strength

Financial strength is an indicator of the amount of business risk that a company is taking. Companies with financial strength will survive the bad times. Debt to equity ratio, quick ratio, and current ratio are measures of financial strength. They are discussed below.

3.2.1.1 Capital Structure

QLTI's high-risk profile is reflected in its expensive capital structure (low financial-leverage), allowing it to engage in risky programs. As a differentiator, QLTI has to take long-term risks and cannot commit to fixed cash flows to repay loans. In Q3 2003, identifying an opportunity in the convertibles market, QLTI increased its debt burden by raising US$ 172.5MM in convertible notes, thereby increasing its liabilities to US$ 201MM and its debt to equity ratio overall. QLTI's ratio of long-term debt to equity for the most recent quarter (MRQ) compares

[32] www.financeyahoo.com

favourably with the biotech / major drugs industries averages; however, some of its competitors have capital structures that are even further geared towards a differentiation strategy.

3.2.1.2 Quick and Current Ratios

Quick ratio and current ratio measure the level of liquidity that is available in a short period of time. QLTI is an outlier with exceptionally high ratios compared with industry averages and its competitors. This creates flexibility, which may enable opportunistic behaviour, but it is expensive to hold assets in short-term instruments, and it increases QLTI's attractiveness as a takeover candidate.

3.2.2 Growth

The first year that QLTI generated positive net income was 2000. Its EPS for the years 2000, 2001, 2002, and 2003, was US$ 0.07, 1.05, 0.2 and 0.65, respectively. The mismatch between the EPS and growing revenues during these years (US$ 32.4, 83.4, 110.5, and 146.8MM, respectively) is due to two factors. First, during 2001 QLTI had a net income that nearly matched its revenues. This was attributed to provision for recovery of income taxes in the amount of US$ 42MM. Second, during 2002 there was a steep increase in costs and expenses compared to 2001 (US$ 83.4MM vs. US$ 68.3MM, respectively), which combined with a negative recovery of income taxes, reduced the net income from US$ 72MM during 2001, to US$ 14MM during 2002. Revenues during 2003 were US$ 45 MM.

With a quarterly EPS growth of 26%, QLTI is well above its industry average. Its quarterly sales growth of 22% is comparable to the biotechnology industry average. It also fares well compared to its competitors in the biotechnology industry and in the vertically integrated pharmaceutical firms. QLT is growing as a result of increased Visudyne® sales. The key to continued growth in the short term seems to be continued growth of sales.

3.2.3 Profitability

QLTI gross profitability ratios are high compared to the industry. The gross margin may reflect the high premium for Visudyne® - the first drug of its kind. It is interesting to note that the operating margin and the net margin for the Biotech industry are substantially higher for the Trailing Twelve Months (TTM) than for the 5 yr average. This may reflect the composition of the biotech industry. Many biotech companies are young and do not have large balanced portfolios. As well, their early years are characterized by low revenues relative to operating expenses. This trend is absent in vertically integrated pharmaceutical firms. Similar to the industry to which it belongs, QLTI's operating margin is substantially higher for TTM compared to its 5 year average. However, as explained earlier, QLTI's net profit margin does not behave in this way.

3.2.4 Management Effectiveness

The average management efficiency ratios, regardless of whether they are TTM or 5 yr average, are higher for vertically integrated pharmaceutical firms than for the biotech. QLTI management efficiency ratios are high compared to the biotechnology industry averages, however, not compared to its competitors or the averages of the vertically integrated pharmaceutical firms.

For the biotechnology industry, similar to the operating and net margin from the above section, management efficiency ratios (ROA, ROI, and ROE) for TTM are higher than for the 5 year average. This trend is reversed for the more established vertically integrated pharmaceutical firms. QLTI reflects the biotechnology trend in that its TTMs are higher than its 5 yr averages. This is due to the higher net income generated during the last year. However, the gap between ROE and ROA or ROI is modest compared to both industry averages, as well as the majority of its competitors. This shows relative lack of leverage.

3.2.5 Efficiency

The vertically integrated pharmaceutical firms are more labour intensive than the biotechnology industry and QLTI is no exception; however, QLTI is also somewhat more labour intensive compared to the average of the biotechnology industry. The trend reverses with regards to capital; vertically integrated pharmaceutical firms are less capital intensive than the biotech. QLTI is by far the most capital intensive of them all.

3.2.6 Summary

QLTI is a biotechnology company with a blockbuster drug. Its sales and revenues are growing fast, providing growth in earnings per share. Its margins are good. Cash is accumulating fast. However, having only one product and rapidly growing assets, the asset turnover is low. Returns on assets and on equity suffer as a result.

Low effectiveness ratios over time could suggest that management is not taking full advantage of assets entrusted to it. Combined with a conservative capital structure, lofty cash reserves, little debt, stable positive cash flow and given the right share price, QLTI is a natural target for takeover. Of note is that QLTI P/E (TTM) ratio is 20.8, a ratio that reflects that the market is expecting a very strong growth from Visudyne® and other products in QLTI's portfolio.

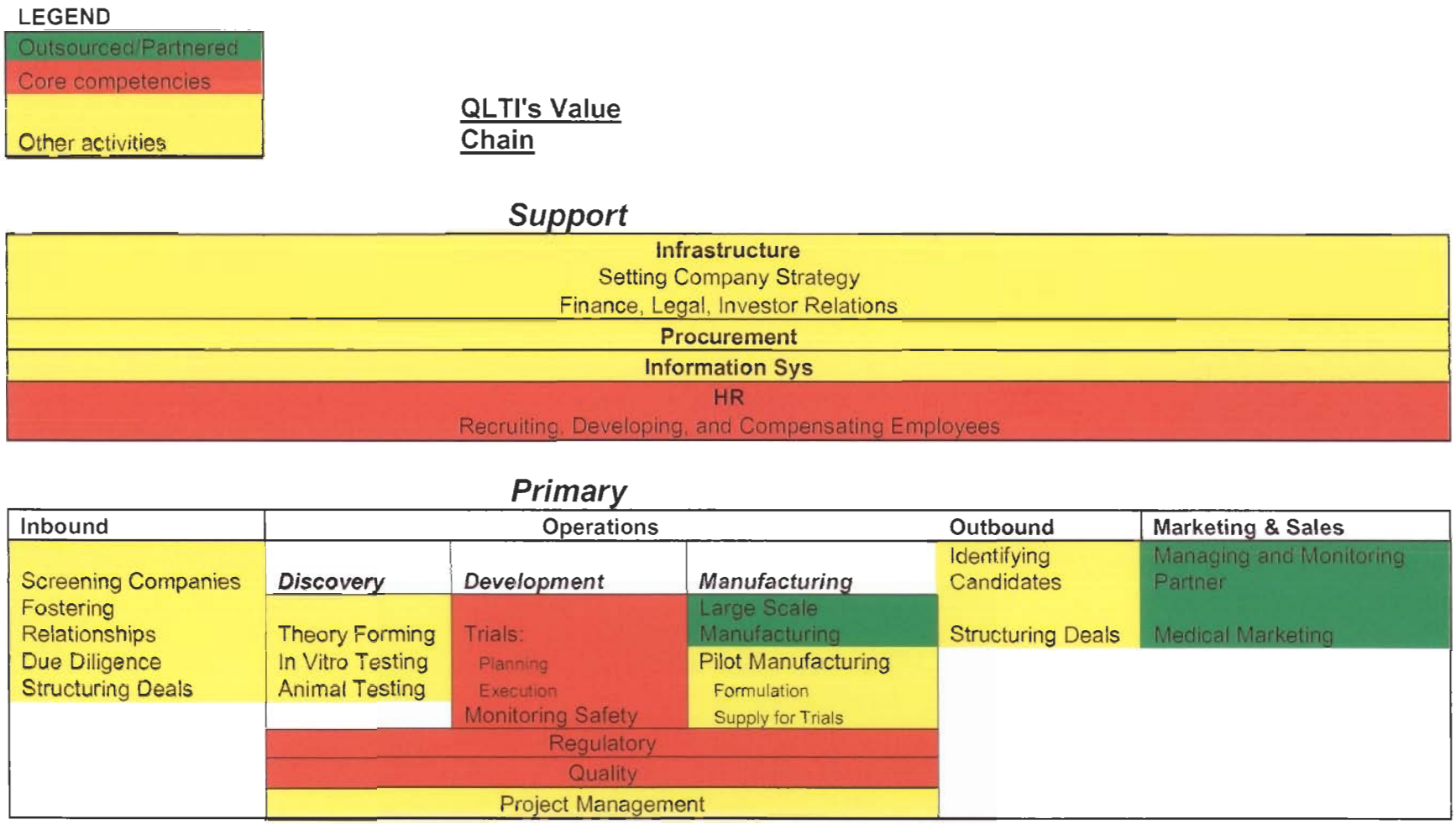
3.3 Value Chain Analysis

QLTI operates in a matrix / project structure. The value chain of the ocular business is superimposed on that of the wider company as will be outlined below. The final product of a QLTI is a chemical entity proven effective and safe for the treatment of a medical condition. The activities that biopharmaceutical firms perform in order to come up with such a product occur at

two levels. The first belongs to the realm of the knowledge industry. It consists of the identification of appropriate drug candidates, their modification or formulation, the provision of proof of their safety and efficacy for a certain disease, and the marketing/selling of drugs to other companies or the public. Hence, value is created as much by proving product has certain attributes, and by positioning the product in the right context, as by changing its physical properties.

The second level of activities is more mundane and common to companies which process physical products. It pertains to receiving, storing, and disseminating the materials necessary to manufacture the drug, its manufacturing and distribution. Activities at these two levels occur in parallel. Inbound and outbound activities in the first level are concerned with handling of knowledge whereas at the second level they are concerned with handling of physical entities. In this paper, the inbound and outbound activities that pertain to manufacturing will be considered as part of the manufacturing process itself. This is reflective of the relative importance of manufacturing in the biopharmaceutical industry.

Figure 3-3 QLTI's Value Chain (*Based on Porter, 1985*)



3.3.1 Primary Activities

The following activities affect the product directly.

3.3.1.1 Inbound Logistics

For QLTI, the desired final products are chemical entities that are proven to be effective and safe for the treatment of disease. The ocular business focuses on NCBE. Inbound logistics are the activities associated with receiving, storing, and disseminating inputs to these products. Inputs are data relating to drug candidates at different stages of development. Activities are primarily led by the business development function, which employs individuals who combine business, science, and legal skill. Business development activities consist of screening, storing information, and contacting companies with relevant compounds. As well, fostering relationships with research institutions is an important action. Once a candidate is identified, due-diligence takes place. The team which evaluates a candidate includes the following functions (most of which will participate in the development process): Clinical Preclinical Science, Clinical Science, Regulatory, Marketing, Legal and Project Management, and Finance. For ocular candidates, the team is the ocular project team. Business Development will also structure the final deal. The value created at this stage consists of the identification of drug candidates that have a high probability of achieving final stages of development, as well as a good fit with QLT's strategy and portfolio.

The agreement between QLTI and Xenova is an example of such activity. In August 2001, Tariquidar, a P-glycoprotein antagonist for multi drug resistance in cancer, was in-licensed by QLTI from Xenova for the North American development and marketing rights.[33] It was identified as a good fit with QLTI development expertise in cancer. Furthermore, its advanced

development stage would have made it a good addition to QLTI's portfolio, as Visudyne® advances in its life cycle. It was deemed to have good probability of success to get approval. The deal was structured so that QLTI would pay Xenova an initial licensing fee of US$ 10MM, and milestone payments up to a maximum of US$ 50MM, in addition to future development costs. Upon commercialization, QLTI was to pay royalties to Xenova in the range of 15-22%, depending on the level of sales.[34] Once the product found its way into QLTI it advanced to the next level of the value chain. As mentioned above, this opportunity proved to be unsuccessful.

Based on publicly available information, to date, no deals were structured to supplement Visudyne® with drugs at an earlier stage of development for the market for NCBE. It is reasonable to assume that many opportunities were and are being evaluated. Given the structure of the industry, the relationship between biotechnology companies and vertically integrated pharmaceutical firms, and the importance of alliances, the competencies QLTI has could provide it with a competitive advantage in this market.

3.3.1.2 Operations

Operations refer to activities associated with transforming inputs into final product forms. In QLTI the materials are drug candidates. The processes that a chemical entity undergoes in order to become approved for marketing, at a designated jurisdiction, fall under the umbrella of operations. These include Discovery, Development, and Manufacturing.

3.3.1.2.1 Discovery

Discovery is the first process that chemical entities undergo on their way to become approved for marketing. The scientists at QLTI's discovery group use the chemical entities which were developed in-house or in-licensed to test hypotheses as to the role that they might play in

[33] www.xenova.co.uk

certain disease processes. Initially, the experiments are performed In Vitro (in an artificial environment outside the living body) and may include chemical modification. Subsequently In Vivo (in the living body) experiments are performed in animal models in an attempt to predict the efficacy and safety of the compound in humans. In order to perform these activities, QLTI employs a group of scientists in the preclinical department who are assigned research areas. A research area may apply to more than one therapeutic field. For example, Angiogensis is a research area that applies both to cancer and NCBE. This is an opportunity for synergism for QLTI. In order to accommodate basic research and discovery, QLTI has an infrastructure of laboratories and an animal facility.

QLTI's collaboration with Kinetek Pharmaceuticals Inc., a Vancouver-based privately-held biopharmaceutical company, is an example of value chain activities at an inbound and discovery level.[35] Since June of 2001, QLTI and Kinetek have collaborated on a research and early development program to develop signal transduction inhibitors for the treatment of eye, immune system and kidney diseases. Kinetek had a unique proprietary position on Integrin-linked kinase (or ILK). Inhibition of the kinase activity of ILK has the potential for broad range of clinical applications, including cancer, inflammation, kidney, and eye diseases. Peer-reviewed published studies of small molecule ILK inhibitors in cancer, discovered by Kinetek, have recently shown that they block tumor angiogenesis and cause tumor shrinkage.

The transaction consisted of an initial equity investment by QLTI of CDN$ 11, or 3.14 million Kinetek common shares to support the research and development. QLTI also had the option to obtain up to three additional compounds through further equity investments of CDN$ 5MM per compound. QLTI's initial equity investment was supplemented by a concurrent investment of CDN$ 5.5MM by a number of Kinetek's existing major shareholders. Once a

[34] QLT Inc. Press Release, 13 August, 2001.
[35] QLT Inc. Press Release, 7 June, 2001.

compound is ready for clinical trials, QLTI has the right to an exclusive license for that compound in the fields of ocular, immune (excluding asthma) and renal disease, in exchange for milestone payments and royalties based on cumulative product sales. At that time, QLTI would take over the clinical development and commercialization of each product, while Kinetek would retain the right to exercise a co-development option for products outside ophthalmology. The total of milestone payments and the initial equity investment were capped at US$ 80.1MM. The milestone payments were based on clinical trial progress, product approvals and sales volumes.

On March 2004 QLTI announced that it would be acquiring Kinetek. Paul Hastings, QLTI's President and Chief Executive Officer, positioned the deal in the following way:[36]

> "As a result of our previous involvement with Kinetek, we are well acquainted with Kinetek's scientific programs,"; "Given QLT's research and development capabilities and resources, we feel the Kinetek science has strong potential in our hands, particularly in the area of oncology, an area of research that we did not have rights to in our collaboration."

Following the deal, Kinetek's compounds became part of the portfolio of QLTI's discovery group.

The value created at the discovery stage includes the ability to correctly apply the drug to relevant *In vivo* and *In vitro* models, and to modify them so that they can be advanced to the clinical stage. During the development of Visudyne®, the preclinical group at QLTI had accumulated expertise in performing and interpreting *In vitro* experiments with photosensitizers. It has the advantage of being one of the first and only groups in the world to do so in an industry setting. Although most of the *In Vivo* animal work in models of NCBE was outsourced, the group nevertheless has experience in managing the vendors and interpreting the results. The group is also involved in due-diligence activities. Discovery in the field neovasculare diseases in

[36] QLT Inc. Press Release, March 29, 2004.

general, and in the eye in particular, is well on its way to become a core competency of QLTI, which can provide competitive advantage in the market and is especially critical for smaller biotechnology companies.

3.3.1.2.2 Development

Development is the second process that a chemical entity undergoes before it is approved for marketing. During that stage, it is tested in humans in strictly monitored clinical trials. The sequence of trials as generally accepted by the regulatory agencies across the world is as follows:

Phase I - Establishes safety in humans. The patient population is a limited group of healthy volunteers (20 – 40). The studies are used to determine toxicity, dosages (formulations and amounts), blood levels, excretion profiles, and pharmacokinetic profiles.

Phase II - Establishes that the new chemical entity is effective in treating the disease in limited patient populations (100 -200 subjects). Phase II is generally when adverse effects of a potential drug are observed. The studies are used to determine toxicity, compatibility with other medications, bioavailability/bioequivalence of different formulations and a variety of other effects.

Phase III - During this phase, a variety of patients with varying degrees of the disease are studied. Multi-center, controlled trials on thousands of patients are run to complete the establishment of safety, efficacy and dosage for the compound.

Phase IV - Post marketing surveillance is used to monitor the drugs efficiency in treating large populations, locate any reports of adverse effects, and assess the relative efficacy of the drug. All public reports about a drug are maintained by the company that markets the drug.

The department that leads these trials in QLTI is Clinical Research. It may very well be the largest department in QLTI, employing a diverse group of people with a broad skill set. The

clinical Science group is structured according to therapeutic areas. The support groups are Medical Writing, Biometrics and Data Management, Clinical Operations, and safety. Individuals are assigned to work on projects in a matrix structure. Overall, activities include the planning and execution of the trials in collaboration with investigators around the world, while adhering to GCP guidelines, as well as the documentation and presentation of the results to regulators. In addition, the Safety group's role is to collect, record, and interprets the adverse events from ongoing trials. The processes must comply with regulatory requirements and are essential to a successful approval.

Currently, the clinical department at QLTI is running several trials at different stages of development:

1. Phase III study of Visudyne® Therapy in Occult with No Classic Subfoveal Choroidal Neovascularization (CNV) Secondary to Age-Related Macular Degeneration (AMD).
2. Phase I/II Dose Escalation Study to assess the safety, tolerability, and preliminary efficacy of transurethral photodynamic therapy with lemuteporfin (QLT0074) for Benign Prostatic Hyperplasia
3. Phase II Treatment Regimen Optimization study of photodynamic therapy with topical lemuteporfin (QLT0074) for Androgenetic Alopecia.

Experience in the specific therapeutic areas and networks are critical to performing trials in a proper way. Importantly, these take years to develop. QLTI does not outsource any of its development activities. The value created at the development stage is the conduct of appropriate human experiments in a timely and efficient manner, which would provide the evidence needed for approval. Errors in this process have serious consequences as this is the most costly and longest stage in drug development. QLTI has developed core competencies in development in the therapeutic areas in which it had been active over the years. Arguably, as a result of the development of Visudyne®, and by virtue of it being the first drug in a disease area, as well as being a success story, QLTI's group is very well poised to apply this knowledge to other drug

candidates. During the development process, QLTI has conducted numerous trials across all stages, some of which are still QLTI's ongoing trials in the area of wet AMD are well known for their high quality and have become the gold standard in the field. Clinical research is *THE* core competency of QLTI and its ocular business, providing it with an important competitive advantage.

3.3.1.2.3 Manufacturing

QLTI has no mass manufacturing capabilities. It outsources commercial manufacturing of Visudyne®. However, to the extent that manufacturing is part of research and development, QLTI has invested in a Pilot Manufacturing Facility (PMF) on site.[37] With its new PMF, the small yet important manufacturing group at QLTI will perform three roles. First, managing and monitoring the outsourced activities; second, enabling quick and independent modifications (formulations) of existing products as part of the discovery effort and; third, producing drug supply for ongoing preclinical and clinical trials. The in-house value created at this stage is the ability to modify the agents or formulate them in ways which would make them more suitable for their purpose, as well as to support ongoing trials in a timely and efficient manner. Mass manufacturing is not one of QLTI's core competencies, thus does not provide a competitive advantage in the market.

3.3.1.2.4 Project Management

Project management was introduced to QLTI's operations during the last 5 years. It is building on experience which was accumulated at QLTI and formalizing existing practices. The created value will be increased efficiency. This relatively new function is yet to become a core competency, and is unlikely to provide QLTI, or its Ocular Business Unit, a competitive advantage in the near future.

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[37] QLT 10-K, p. 8

3.3.1.2.5 Regulatory and Quality

The biopharmaceutical industry is a heavily regulated environment. Therefore, regulatory and quality activities are critical during all the operational activities (*i.e.,* late stages of discovery, development), and manufacturing. QLTI has an internal group with competencies in these areas. This group ensures that the processes are conducted in compliance with the regulatory requirements. The regulatory process mandates communication and periodical meetings with regulatory agencies. Importantly, at the end of the phase III (Pivotal) trials a New Drug Application (NDA) is submitted and reviewed by the regulators. This part is a significant undertaking, which can take up to two years from start of preparation to approval. The value that the regulatory group adds is essential in preventing delays and errors in trial conduct, and is critical in the proper presentation of results. The fact that QLTI has never had an unsuccessful submission testifies to the high standards exhibited by this group. Similar to the clinical group, the regulatory group has accumulated significant experience with the ophthalmic divisions of the world's regulatory agencies. It is familiar with specific requirements and personalities. Regulatory Affairs, as it relates to NCBE, is thus a core competency at QLTI, and a source of competitive advantage.

3.3.1.3 Outbound Logistics

Outbound Logistics refers to the sequence of material shipment outside of the business. In the context of this value chain, it means structuring deals that result in generating revenues. The value created at this stage consists of the identification of proper customers or partners for consummating a deal, which fits best the parties' interests, and has the greatest chance to last, and its execution.

It is noteworthy that in this value chain, products gain incremental value as they are being processed, regardless of the point at which they enter or exit. Hence, a drug candidate may enter

the chain at any of the several stages of development, or exit at different stages of maturity. This provides a much welcomed flexibility to the value chain, making inbound and outbound activities applicable along the chain. For example, while Photofrin, the world's first approved photodynamic therapy agent which was developed and commercialized by QLTI for use in various cancerous conditions, was sold on June 8, 2000, to Axcan Pharma, Visudyne®'s commercialization rights were retained by QLTI, which, in turn, entered into an alliance with NVO. QLTI, and in particular its ocular group, had developed significant skill in managing the relationship with NVO. The relationship had worked well thus far and withstood significant challenges, one of which is the partnership between NVS and DNA to develop Lucentis™, Visudyne®'s competitor. Hence, a core competency of the ocular business unit is working in an alliance environment. Given the realities of the biopharmaceutical market, this constitutes a must.

3.3.1.4 Marketing and Sales

QLTI entered a strategic alliance with NVO for the exclusive commercialization of Visudyne®. Consequently, QLTI's marketing activities are focused on managing and monitoring its partner's activities. Because QLTI holds the most extensive body of knowledge with respect to Visudyne®, NVO looks to QLTI for input to Medical Marketing activities, which involves physician and patient education. Significantly, because QLTI is Visudyne®'s manufacturer, it is responsible for the continuous safety monitoring. Although of some use in the context of an alliance, the marketing competencies of QLTI (or lack thereof) cannot provide it with a competitive advantage.

3.3.2 Support Activities

The following activities support the entire chain and not its individual components.

3.3.2.1 Infrastructure

The primary objective of QLTI is to increase its value. Executive management, investor relations, finance, and legal, are all entities intended to add value indirectly, by supporting the primary activities. The exceptions to this rule are the subsets of finance and legal, which are involved in primary activities. They provide specialized expertise which is valuable in the inbound and outbound logistics. The evaluation of new products includes valuation and determination of IP position as well as structuring the correct legal framework. When a product is outbound for or partnership with another company, similar activities take place. These directly activities add value to products which the company make, and can be considered part of the primary activities.

3.3.2.2 Human Resources (HR)

The activities of HR are to recruit, develop, and retain employees. Employees hold knowledge critical to the success of the company. For this reason, HR's role in the biopharmaceutical industry is especially important. HR in QLTI is successful in making employee's satisfaction a companywide priority. This resulted in the implementation of a variety of initiatives outlined in sections 3.1.6 and 3.1.7. Noteworthy initiatives include: encouraging diversity in the workplace, encouraging mobility of employees across functions in order to enhance flexibility; the offering of a variety of internal courses; entitlement to attend external training and conferences; truly flexible working hours and the ability to work from home; comprehensive benefits package, linked to performance; scholarships for continuing education; on site family room and gym and; a subsidized cafeteria.

QLTI does not outsource its core HR functions which are described above. It does call upon external resources for exceptional tasks (like training). Given the importance of human

capital in the biopharmaceutical industry and the track record of this function at QLTI, it seems that HR can be considered a core competency at QLTI and a source of competitive advantage.

3.3.2.3 Information Systems and Procurement

QLTI has an IT department which leads decisions for purchasing and managing information systems. SAP, an Enterprise Resource Planning system, was recently put in place. These systems are standard across industries, and are not specific to the company's primary value adding activities. IT is essential to the proper functioning of most companies in this day and age, and more so in the knowledge industry. Consequently, this activity is not a source of competitive advantage.

Procurement refers to purchasing of materials which are used in the company's value creating activities, for example, laboratory equipment. Although QLTI does not outsource these activities, just like information systems, these activities are fairly standard across the biopharmaceutical sector and thus, are not a source of competitive advantage to QLTI.

3.3.3 Summary

QLTI creates value by identifying drug candidates at different stages of development; accessing them by acquisition or another arrangement; associating them with a therapeutic areas and disease processes; modifying them to better suit its actions and; performing the necessary activities to prove the safety and efficacy. This is a knowledge intensive process. Value is incrementally added as products move along the chain.

The value chain analysis identifies operations, and especially clinical development in the ophthalmic area, as *the* core competencies in QLTI. This is the source from which QLTI has drawn its competitive advantage. HR is a core competency that relates to support activities.

While the industry's value chain contains many other components, these two are the most important in the biopharmaceutical industry. Whereas other companies have to partner or outsource to get access to these competencies, QLTI has them *in-house*.

Importantly, QLTI must be able to compete in the same field with vertically integrated pharmaceutical firms. To achieve this goal, it must strengthen discovery to the degree that would provide a competitive advantage and synergize with development. Inbound and Outbound logistics are also critical activities. For QLTI, the discovery of Visudyne® foremost, followed by its partnership with NVO, provided the entry ticket to the industry. This highlights the importance of discovery and business development.

3.4 Conclusion

The objective of the internal analysis was to shed light on the competencies at the disposal of QLTI's ocular business. This was performed in the context of the industry analysis, which identified the germane competencies necessary to maintain a competitive position in the industry for NCBE and touched on the biopharmaceutical industry in general.

QLTI manifests many competencies typical of a biotechnology company. With the exception of a somewhat centralized decision making process, its footprint fits a differentiation strategy. Its capital structure is conservative and well suited for a high risk profile. The sales of its innovative product, Visudyne®, fuel the much expected rapid growth on the one hand, but the accumulating cash constitutes an underutilized asset on the other. Value chain analysis reveals clinical development, in particular for NCBE, as the most prominent core competency and a relative weakness in discovery.

According to the majority of it characteristics QLTI is still a biotech company. Although it has a successful block buster product and positive cash flow, it does not possess the

competencies of vertically integrated pharmaceutical firms. Yet, the most critical element of a biotech, namely, core competency discovery, seems to be out of steam.

The next chapter will identify issues that the ocular franchise of QLTI is facing. The strengths and gaps which were outlined in this chapter will have an implication on the ability to meet these challenges.

4 ISSUES

This chapter outlines the challenges that QLTI's ocular franchise faces. In doing so it draws upon the information provided and analysis performed in the previous chapters. Some of the issues are outside the control of QLTI, others are more closely linked to the gaps identified in the previous two chapters, and others still are the gaps themselves. The challenges are presented according to the order in which their effect is expected to become evident.

4.1 Short-Term Challenges: the Loss of Visudyne®'s Exclusivity in the NCBE Market

Since April 2000, when Visudyne® was granted marketing approval in the US and subsequently in other parts of the world, it enjoyed exclusivity in the market place. It was the only available pharmacological treatment for wet AMD. This exclusivity led to numerous intangible and tangible benefits. With the first hints of the drug's efficacy in the treatment of the unmet need, entry barriers were immediately lowered. The regulators and the public were eager to accept any improvement to the "no treatment" status quo. Vertically integrated pharmaceutical firms were anxious to enter an alliance and provide capital, in expectation of high returns. Physicians and patients were happy to take part in clinical trials. Most importantly, marketing was straightforward. There was no need to emphasize special attributes of Visudyne®. For example, an advertisement placed by NVO in one of the leading peer reviewed ophthalmology journals reads

"Central to sight in CNV, Visudyne helps patients to maintain visual acuity and contrast sensitivity."[38]

Impact on patients' visual function is unlikely an attribute specific to Visudyne®; any drug in this disease area would have to pass this regulatory hurdle in order to get approval. Compare this to the following advertisement, taken from the same journal, and also by NVO, but referring to a drug for the treatment of allergy:

"Zaditen - rapid and long lasting relief" (Zaditen by NVO).[39]

In this example relief is taken for granted. It is the special nature of this relief, rapid and long lasting, which is emphasized. Other examples are the advertisements referring to drugs for the treatment of Glaucoma:

"Only XALATAN.... is First Line Approved Among Ophthalmic Prostaglandins" (Xalatan by PFE)[40]

"The One to Start On; The One to Stay On" (Xalatan by PFE)[41]

"Good Enough" may not be low enough" (referring to intraocular pressure) (Lumigan by AGN)[42]

Drugs marketed in a competitive environment are positioned relative to competitors, referring to their special characteristics. Visudyne® was unique, and differentiated itself by the mere virtue of being available.

However, in all likelihood change is around the corner. As outlined in sections 1.5 and 2.1.3, Macugen™ and Lucentis™, threaten to put an end to Visudyne®'s exclusivity in the market place.

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[38] *Ophthalmology*, Volume 111 Number 9, September 2004
[39] *Ophthalmology*, Volume 111 Number 9, September 2004
[40] *Ophthalmology*, Volume 111 Number 4, April 2004
[41] *Ophthalmology*, Volume 111 Number 8, August 2004
[42] *Ophthalmology*, Volume 111 Number 5, May 2004

4.1.1 Products and Competitors

Macugen™ and Lucentis™ have mechanisms of action different than Visudyne®. The latter exerts its effect by immediate closure of blood vessels in the CNV. Both Macugen™ and Lucentis™ target Vascular Endothelial Growth Factor (VEGF), a protein that has been shown to play an important role in the abnormal blood vessel growth and leakage associated with wet AMD and DME. Macugen™ and Lucentis™ bind to VEGF, inhibiting its function. As these products share a similar mechanism of action, in all likelihood if one of them is proven to be effective, so would the other.

Similar to Visudyne®, Macugen™ and Lucentis™ are developed by two alliances, each between a biotech and a vertically integrated pharmaceutical firm: Macugen's™ alliance is between EYET and PFE. EYET brings to the partnership a team of renowned scientists with ophthalmic and vision research expertise, while PFE brings the marketing muscle of the world's largest and most valuable pharmaceutical. Lucentis'™ alliance is DNA and NVO. DNA, one of the world's leading biotechnology companies, is leveraging its expertise in the field of vascular biology, while NVO's primary contribution is its experience with the development and marketing of Visudyne®.

4.1.2 Timelines

The launch of Macugen™ and Lucentis™ present the most immediate and real threat to QLTI's wet AMD business. They are likely to enter the market in a stepwise manner. EYET has already presented positive results from its pivotal trials, and filed a New Drug Application with the U.S. regulators. Macugen™ may become available in the US as early as the first quarter of 2005. Pivotal trial with Lucentis™, conducted by DNA and NVO, are still ongoing. Approval and launch are expected in the last quarter of 2006.

4.1.3 Impact on the NCBE Market

The structure of the market NCBE was discussed in section 2.2. The availability of a few approved drugs in this market is likely to have an effect on some of the forces described. Suppliers, as well as buyers, will now enjoy an increasing number of options, enhancing their bargaining power with the competitors. Specialized labour will enjoy increasing demand. Companies will have to compete for the participation of a relatively small and constant supply of academic sites and their patients in post-marketing trials. As to the buyers' side, competition between the companies to access society's resources will undoubtedly increase. For example, a third party payer (an insurer) may decide to cap reimbursement per patient, per year, thus denying patients the option to try a different drug if the one they are using fails to ameliorate their condition. Another potential scenario depends on the need of patients to combine the different treatments within one full treatment course. Under these conditions, companies would be hard pressed to lower the price of their drug, thereby allowing patients to collect reimbursement for an entire course, and increasing the patients' motivation to choose their drug. All of the above factors confirm that the competitors are most likely to face increased rivalry among them, which is likely to lead to reduced profits.

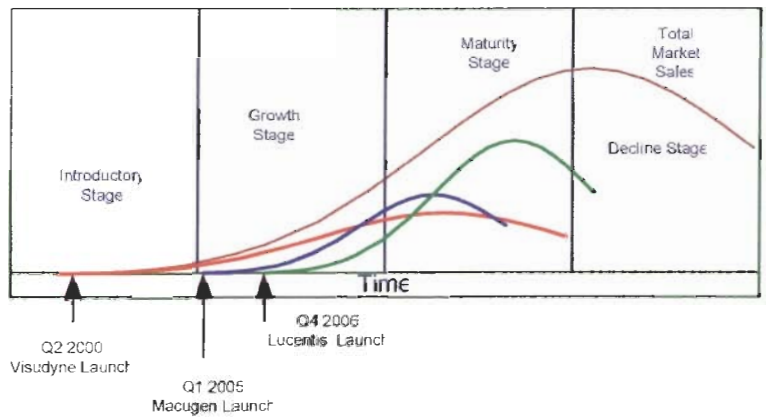
4.1.4 Impact on Visudyne® sales

Visudyne®'s growth in sales can be attributed to the following factors: increased penetration, increase in the number of affected patients due to aging population, and higher rates of diagnosis due to raised awareness and superior screening methods.

Currently, Visudyne® owns 100% of the treated market. However, as is illustrated in Figure 4-1 Potential Impact of New Entrants in the NCBE Market on Visudyne® sales, new entrants to the market are likely to stand in the way of Visudyne's® future penetration. For

example, Macugen's™ sales could surpass and take away from Visudyne's® sales, due to a more favourable label that includes all lesion types, without lesion size limitation. Lucentis™ may surpass the latter due to a superior efficacy perception. A bite in Visudyne®'s future market share, may adversely affect the growth of the ocular business in QLTI and, given that its QLTI only commercial product, the growth of the company as a whole.

Figure 4-1 Potential Impact of New Entrants in the NCBE Market on Visudyne® sales



4.1.5 Impact on QLTI's Alliance with NVO

In June 2003, NVO entered an agreement with DNA for the development and commercialization of Macugen™. This agreement was signed 8 years after NVO had entered its agreement with QLTI, and while Visudyne® sales were still growing. Fulfilling the obligations arising out of these two agreements to market two competing products constitutes a conflict of interests for NVO. This is particularly evident outside North America, where marketing and development rights overlap. This is further compounded by the fact that Macugen™ and Lucentis™ share many characteristics. Consequently, NVO's ability to respond to the immediate threat of Macugen™, by launching an effective and credible marketing offensive, is likely to be compromised. A marketing message that would reflect negatively on Macugen™, in comparison

to Visudyne®, may reflect negatively on Lucentis™ too. Hence, NVO may refrain from emphasizing significant disadvantages of Macugen™ such as its inferior safety profile, resulting from the need to repeat intraocular injections. Since QLTI relies exclusively on NVO for the marketing of Visudyne®, NVO's agreement with DNA creates a serious issue for QLTI.

4.2 Intermediate Term Challenges

4.2.1 Underutilized Assets

QLTI experienced substantial growth during the last four years as a result of increased Visudyne® sales. In addition, in 2003, it raised US$ 173MM in convertible notes constituting just short of a third of its total assets. Yet, financial analysis reveals relatively modest effectiveness and efficiency ratios.

At 8.54%, QLTI's ROI (TTM), which accounts for the total funds in the balanced sheet, is at the low end compared to its competitors. Similarly, its absolute return to shareholders, its ROE (TTM), is only 11.75%. These ratios are the result of low efficiency ratios. In particular, with an asset turnover (TTM) of 0.26, QLTI is by far the most capital intensive of all its competitors.

Value chain analysis revealed significant infrastructure, capable of addressing most of the activities of the biopharmaceutical industry value chain. Yet, the number of NCEs that pass through the chain is modest in all therapeutic areas, including NCBE.

Effectiveness ratios measure corporate operating performance. The modest ratios suggest that QLTI is not taking full advantage of the equity of its shareholders and its total funds. It had earlier been pointed out that the combination of poor operating performance, a conservative capital structure, lofty cash reserves, relatively little debt, and prospects of stable positive cash

flow makes QLTI a suitable target for takeover. Underutilization of assets as a whole is related to lack of a substantial portfolio in the ocular business, as well as in other therapeutic areas.

4.2.2 Sustainability of the Ocular Franchise

4.2.2.1 Product Portfolio

The ocular business of QLTI is composed of a single product, Visudyne®. This puts into question the sustainability of the ocular franchise, and raises the doubt whether QLTI is leveraging its current position in the NCBE industry to the best interest of its shareholders.

The emergence of the NCBE industry is established. Any new drug must overcome regulatory barriers and acceptance by physicians and patients, which constitute the introductory stage of the product life cycle. Yet, it appears that the industry as a whole is currently at its growth stage. The industry is exhibiting innovation. New products are emerging; the consumer base is growing.

The lack of a portfolio impacts the ocular franchise and QLTI in several ways. First and foremost, the mere existence of a franchise is fragile when it depends on a single product. As science advances, it is likely that products with a superior value proposition will enter the market, making Visudyne® obsolete. Even if the product keeps having a role in the market, the patents that protect it are bound to expire. The result would be a sharp decrease in price, a result of the competition it will face from generic alternatives. A decrease in price will lead to a decrease in profitability. Since, Visudyne® is, as of yet, QLTI's only commercial product, the results will be grim to the company as a whole.

QLTI have accumulated considerable intellectual capital during the development and launch of Visudyne®. The ocular group has developed considerable expertise in the area of wet

AMD, in particular, its clinical research and development group, but also other value chain elements, like discovery and regulatory. Moreover, because of the commonalities between wet AMD and other diseases (see section 1.6), this expertise could be extended to the whole area of NCBE. Left unused or underutilized, this body of knowledge will dissipate.

4.2.2.2 Brand Awareness

In February, 1995, more than 5 years prior to its launch, QLTI surrendered the rights to sales, marketing, and distribution of Visudyne® to NVO as part of a collaboration agreement between the two. This agreement stands in sharp contrast to another agreement, within the same industry. This latter agreement, between EYET and PFE allows EYET to co-promote Macugen™ in the United States. Moreover, EYET would also be entitled to participate in selling PFE's product, Xalatan®, for the treatment of glaucoma in the United States. In fact, even prior to the approval and launch of Macugen™, EYET and PFE logos already appear side by side. Notwithstanding their drug is not approved for marketing as of yet, in a recent advertisement, published in an ophthalmic peer reviewed journal, EYET and PFE together inserted a promo for their future product.[43] In marked contrast, since Visudyne's® launch, in April 2004, QLTI's logo has never appeared in an ophthalmic peer reviewed journal.

Simply put, brand awareness is the proportion of target customers that recall a brand. QLTI suffers from very low brand awareness in the ophthalmic marketplace. In contrast to some of its competitors, and notably, in contrast to EYET, QLTI never positioned itself as an ophthalmic company.

Externally, brand awareness affects the customers. Although, this does not necessarily bear on Visudyne®'s sales, it does have an impact on QLTI's leverage with physicians,

[43] Ophthalmology, volume 111, number 9, September 2004

specifically, in relations to research collaborations. Importantly, lack of market awareness may be perceived as lack of commitment to a particular therapeutic area, thereby turning-off potential specialized business partners. Future employees may fail to see prospects in their area of expertise within the company. Internally, lack of brand awareness may have a subconscious effect on prioritization and allocation of resources, as well as to affect current employees that derive their expertise from this area. Finally, when, and if QLTI will be introducing a second product to the market of NCBE, and assuming it would do so under its own brand, it will be starting at a potential disadvantage; it will be perceived as a new entrant that still has to prove itself in this highly-specialized area. Overall, the lack of market awareness decreases the sustainability changes of the ophthalmic franchise at QLTI.

4.3 Long Term Challenges - Stuck in the Middle of the Biopharmaceutical Value Chain

Biopharmaceutical industry value chain analysis reveals that the industry is not homogeneous. Biotech and vertically integrated pharmaceutical firms coexist side by side in a symbiotic relationship. Generally speaking, the core competencies of these two categories of companies are skewed towards opposite ends of the industry's value chain, so that biotechs have a stronger footprint on the discovery side, while the footprint of vertically integrated pharmaceutical firms is weighted towards marketing and sales. The gap in the core competencies of the two explains the propensity of alliances between them. The industry for NCBE is an excellent example with all three leading products being developed by an alliance between a biotech and vertically integrated pharmaceutical firm.

QLTI's value chain analysis identifies operations, and especially clinical development in the ophthalmic area, as its core competencies. However, at the same time, it identified a gap in discovery. The gap exists in the ocular therapeutic area as well as other areas, and is manifested

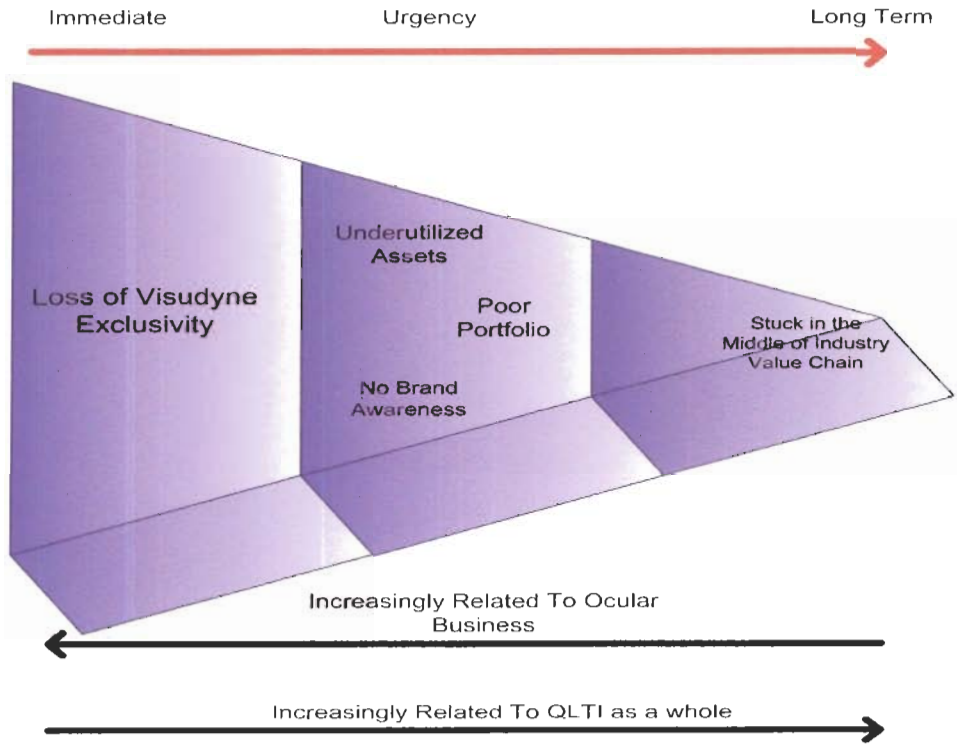
by the lack of progression of NCE from the discovery section of the value chain to the clinical one.

Key success factors in the biopharmaeutical industry in general, as well as in the industry for NCBE in particular, fit well with the characteristics of the biotechs on the one hand, and the vertically integrated pharmaceutical firms on the other. Capital and scale are held by the vertically integrated pharmaceutical firms while innovative products are the bargaining chip of the biotech. Undoubtedly, QLT is a biotech. However, it demonstrates relative weakness in discovery, but does not have any core competencies in sales and marketing to counterbalance its weakness. Hence, QLTI must take care not to find itself in no man's land.

4.4 Summary

Several strategic issues were identified for QLTI, based on the industry analysis and an internal analysis. Figure 4-2 Strategic Issues Facing QLTI and its Ocular Business, illustrates these issues in terms of urgency, and their relatedness to the ocular business and QLTI as a whole. The next and final chapter will outline recommendations to address the identified challenges.

Figure 4-2 Strategic Issues Facing QLTI and its Ocular Business



5 RECOMMENDATIONS

This concluding chapter outlines various recommendations that address the challenges and issues raised in the previous chapter. Like the previous chapter, it too draws upon the information provided and analyses performed in chapters 1, 2, and 3. The industry requirements and business competencies frame the recommendations and dictate their execution timelines.

5.1 Leverage the Entry of New Products to the NCBE Market

The most urgent problem that QLTI's ocular business faces is an imminent entrance of competing products to the wet AMD market. While new products do pose a threat, it is possible, and even desirable, to leverage this development in two important ways.

5.1.1 Enhance Product Differentiation

The first opportunity that competition provides is to enhance differentiation. Competitors can serve as a standard of comparison, revealing the special attributes of, and differences between, the offerings. Buyers will have to make choices and therefore be more attentive to specific value propositions. The first step is to identify the special product attributes of Visudyne® compared to its competition. Importantly, its must be viewed from a consumer perspective, and should relate to his or her decision-making processes. Table 5-1 Comparison of Product Attributes between Visudyne® and new entrants represents such an attempt. There are two consumers of interest: patients and physicians. The relative importance of the attributes is likely to be different for each of them. While to both, safety and efficacy are of utmost importance, the mode of delivery is likely to be more critical to patients than to physicians. The

opposite may be true for the mechanism of action, an area where patients tend to defer to their physician's recommendation.

Table 5-1 Comparison of Product Attributes between Visudyne® and new entrants

Product Attributes	Visudyne®	Macugen™	Lucentis™
Efficacy	=	=	?
Safety	Well Established track record. On the market for 5 years.	Likely to be perceived as lower than Visudyne® due to invasive mode of Administration	Likely to be perceived as lower than Visudyne® due to Mode of Administration
Mode of Delivery (or Administration)	Intravenous followed by Laser. Long, but not uncomfortable.	Injections into the eye. Short and uncomfortable.	Injections into the eye. Short and uncomfortable.
Frequency of Administration	Every 3 months. Average of X during first year and Y during the second.	Every 6 weeks. Duration remains to be determined.	Every 4 weeks. Duration remains to be determined.
Mechanism of Action	Immediate shutdown of neovasculature.	Cessation of leakage and prevention of CNV growth	Cessation of leakage and prevention of CNV growth
Impact on Physician's Clinic	High - lengthy procedure. Special laser needed. Special Imaging needed for follow up.	Low - Quick procedure. No special equipment needed for treatment. Less onerous imaging techniques are needed for follow up.	Low - Quick procedure. No special equipment needed for treatment. Less onerous imaging techniques are needed for follow up.

The second step is to convert the product attributes to effective marketing messages. The messages should emphasize the unique features and attributes of Visudyne®, and position it compared to the competition. The advantages in safety, mode, and frequency of administration must be emphasized and clearly communicated. The statement below serves as an example:

"Visudyne®, the *only intravenously* approved treatment for....."

Product differentiation does not have to stop with the existing attributes of Visudyne® compared to Macugen™ and Lucentis™. The discovery and development should incorporate elements which would further enhance its unique value proposition. For example, it is well established that a lower frequency of treatments is perceived as a competitive advantage by physicians and patients. Consequently, clinical trials should be designed to examine whether this relative attribute could be enhanced further, by proving that indeed, a smaller number of treatments would suffice. Similarly, development programs could be put in place to address advantages that Macugen™ and Lucentis™ are perceived to have vis-à-vis the need for less onerous imaging procedures.

Addressing the impact and economics of treating large number of patients with Visudyne® on an ophthalmologist clinic is particularly important, since the competitors have an advantage in this regard. The mode of delivery of Macugen™ and Lucentis™ is faster and less labour intensive. Consequently, QLTI should strive to differentiate Visudyne® by providing physicians superior service and support by way of assisting the physicians to set up their clinics to accommodate large volumes of Visudyne® patients. The mandate of NVO's sales representatives should be expanded to allow the provision of customized and clinic-specific advice in this regard. Such advice can address the following issues: does the particular jurisdiction allow a registered nurse to set an I.V. line to patients or would a physician need to be present? Should the physician offer services in a single clinic or several satellite clinics? Must a laser be purchased for each of the clinics? Are there options available for sharing a clinic or expenses with other retinal specialists? A comprehensive and detailed plan to optimize resources should be offered to physicians, much like the way an architect works with a homebuyer. Similarly, physicians' access to lasers should not be a bottleneck, thus tipping the balance in favour of switching to the alternative therapy.

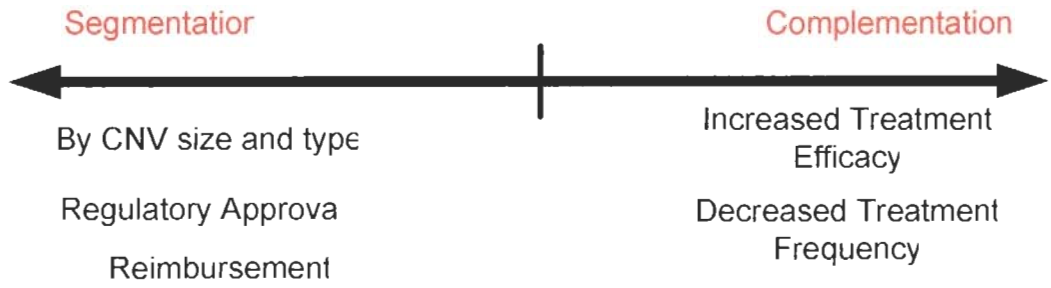
The differentiation of Visudyne® compared to Macugen™ and Lucentis™ is facilitated by the fact that whereas the two are similar in many ways, they are very different from Visudyne®. Consequently, differentiating Visudyne® from Macugen™ first, as it is likely to be the second drug in the market, will have a spill-over effect on the differentiation from the subsequent entrant Lucentis™. Thus, it would help to sustain the value proposition of Visudyne® compared to its competitors.

To execute this recommendation QLTI can rely on its existing core competency in ocular clinical research. The knowledge regarding Visudyne's® attributes and potential resides in QLTI. The clinical team at QLTI must channel some of its resources to support strategic marketing planning. This strategy must have a buy in from NVO since ultimately implementation will depend on its sales force by way of communicating the messages. NVO has an incentive to collaborate in the short run at a worldwide level and in the long run in the North American continent where it does not have Lucentis™ marketing rights. The negotiations with NVO must clearly highlight the common interests, however, QLTI must also be firm, hinting to the consequences of a break in the relationship to the ocular franchise of both parties.

5.1.2 Influence Market Segmentation and Industry Structure

The second opportunity that competition provides is to opportunity to influence market segmentation and industry structure. The arrival of a new product can push the market in two possible directions. The first direction is the triggering of segmentation. The second and opposite direction is by finding a way for the products to complement each other (Figure 5-1 New Products may Pull the NCBE Market in Different Directions). The prospective entry of Macugen™ and Lucentis™ provides an opportunity to go both ways. The players in the field can influence to which way the market would lean.

Figure 5-1 New Products may Pull the NCBE Market in Different Directions



Different product attributes are likely to appeal to different buyers. Market segmentation is concerned with identifying differences in buyer needs, and allowing a company to serve those segments that match its capabilities. Hence, segmentation of the wet AMD market pursuant to the disease different profiles may prove fruitful. For example, Visudyne's® efficacy profile is considered related to the CNV characteristics.[44] Whereas its efficacy for PC lesions is established, its efficacy for MC and OC lesions is still debated. Overall, it is believed to be more effective for PC lesions and for MC and OC lesions with smaller size.[45] Consequently, regulatory approval and reimbursement for Visudyne® is not uniformed across the world. Although it does not appear as if Macugen™ is more effective than Visudyne® for the treatment of PC CNV, it is likely that Macugen™ will have a more favourable label which will include all lesion types, without lesion size limitation. Marketing approval and reimbursement are barriers to market penetration. Lack of marketing approval prohibits active promotion. Hence, even when the drug is available in the market for another indication, it cannot be promoted for off label use. Furthermore, reimbursement is a barrier for penetration for pricy drugs. Given the perceived differences in Visudyne's® efficacy, combined with regulatory and reimbursement profiles, it is possible to achieve segmentation of the wet AMD market according to these criteria, and such segmentation can be pursued strategically in the face of the new entrants.

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[44] Blinder, *supra,* note 3

It is also established that Visudyne® and the new entrants, Macugen™ and Lucentis™, have different mechanism of actions. Furthermore, the efficacy of Visudyne® and Macugen™ leaves a lot to be desired for. The products only help patients to maintain visual function. In fact, patients continue to lose vision, albeit, at a slower rate compared to patients who are not receiving any treatment. Although Visudyne's® treatment administration is not straightforward and is quite cumbersome and lengthy compared to Macugen™ and Lucentis™ , it is nevertheless more patient-friendly: the competitors are administered by way of an injection into the eye, which is a risky and unpleasant procedure. Consequently, marketing campaigns should target patients, and emphasize its relatively safer and less painful mode of delivery.

Given the scientific knowledge thus far, and based on practical facts, the two treatments have the potential to complement each other. Such a combination could arguably result in an increase the efficacy profile on the one hand, and reduce the number of drug administrations on the other. The burden to patients, physicians, and the system as a whole would be smaller. Although a combination therapy reduces the number of the overall treatments for each patient, all competitors may well end up better off. As mentioned above, as the population ages, the market for NCBE drugs is growing. Furthermore, the increased awareness and better diagnosis tools also result in a bigger pool of patients that are in need of a drug. There may well be no apparent need for segmentation. The potential for a combined therapy also contains a solution for NVO's apparent conflict of interest, and may alleviate the tensions between QLTI and NVO due to the latter alliance with DNA.

The combined therapy provides an opportunity to temporarily (at least until the emergence of yet other treatment options) affect the industry structure. It will likely to reduce rivalry among the competitors, ensure better treatment outcomes for patients, and aligns their interests vis-à-vis suppliers and buyers.

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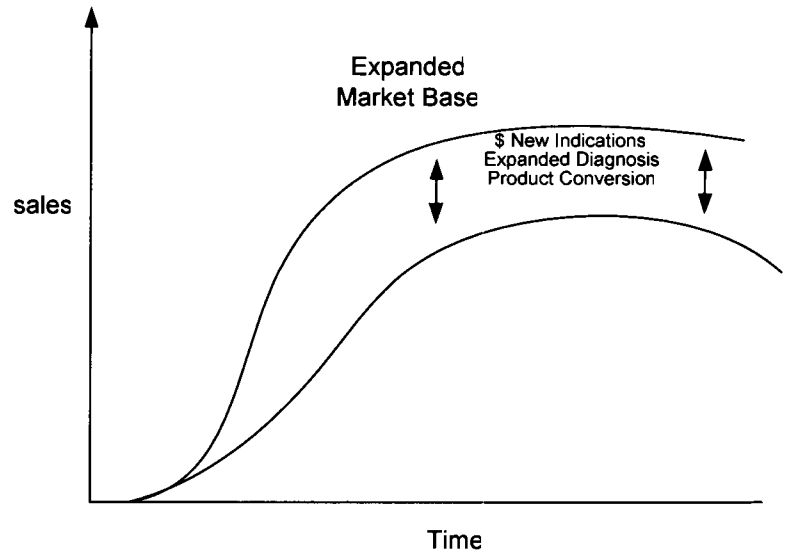
[45] *Ibid.*

As with product differentiation, discovery and development should incorporate experiments and trials, which would test the hypothesis that the drugs, with different mechanism of actions are indeed complementary. This plays directly to QLTI's ocular business core competencies in clinical research. Visudyne's® development program should include a clear objective to research the feasibility of combination therapy with the highest priority. As with the differentiation strategy, it would help to have a buy in from NVO. For NVO, combination therapy would be an elegant way to resolve its inherent conflict of interests. However, in the development dimension QLTI is not dependent upon NVO for the implementation of the strategy. In the face of lack of collaboration from NVO the ocular business at QLTI must convince QLTI's management to allocate resources independently.

5.2 Optimize Visudyne's® Life Span

Optimization of Visudyne's® life span can serve as first strategy to address the threat to the sustainability of the ocular franchise at QLTI.

Figure 5-2 Optimized Visudyne Life Span



$ New Diagnosis are Part of QLTI's Ongoing Strategy (section 3.3.1.2.2)

Based on Simon and Kotler, 2003,

5.2.1 Expanded Diagnosis

The growing number of patients diagnosed with a disease expands the market base. Typically, increased diagnosis means earlier detection. For wet AMD patients, earlier detection goes hand in hand with smaller lesion size. Patients with smaller lesions are more likely to benefit from Visudyne®.[46]

QLTI should proactively pursue and support the development of technologies that enable earlier detection of the disease. One such company is Notal™ Vision, which developed a Preferential Hyperacuity Perimetry™ (PHP™), a device which allows doctors to offer their patients a simple examination for the early detection and monitoring of AMD.[47] Support and

[46] Ibid.
[47] www.notalvision.com

collaboration with a company such as Notal, in addition to expanding wet AMD market base, could provide QLTI with increased presence and brand awareness in the NCBE market.

5.2.2 Product Extension

Product extension is a strategy to strengthen and renew the ocular franchise. Product extension can be attained through patent extension, which adds long term exclusivity, and protects against generic versions. However, perhaps more significantly, product extension should be pursued through product conversion or product reinvention. QLTI should leverage its discovery arm and expertise in the photosensitizers and photodynamic therapy to come up with a successor to Visudyne® with superior qualities. Importantly, the discovery and development of the product's second generation has to be supported at the outset with a publication stream that will prepare the market. The benefits of a product renewal strategy are multiple. The incumbent (existing) product gains from the publicity and interest that are generated from the anticipation for the new product during its development, while the successor benefits from the market presence of the predecessor by way of brand awareness. Most importantly, the franchise is maintained.

5.3 Expand the ocular Portfolio through Acquisitions and Alliances

Expansion of the ocular portfolio is the second strategy to address the sustainability threat to the ocular franchise at QLTI. QLTI and its ocular business are struggling with the 'one drug syndrome'. While this may be acceptable for a small firm, and even typical of biotechs, it is not viable for the long term. Although the long term solution must be the strengthening of QLTI's discovery capabilities, in the short run, a practical and attainable solution may be found in licensing or alliances.

It is not uncommon for biotechs to leverage revenues from a successful product in order to strengthen a franchise and build a family of products. For example, DNA built an oncology

franchise by sourcing Rituxan from IDEC and Teraceva from OSI, to supplement its own breast cancer therapy, Herceptin. In order to take full advantage of Visudyne's® momentum and prevent gaps in its ophthalmic portfolio, QLTI must target products at an advanced stage of development in the short term. To acquire an advanced product, QLTI must be willing to pay a premium. Unless QLTI ensures continuity in its ocular pipeline, its position in the NCBE market is likely to be lost.

Building a sustainable portfolio does not require relatedness in products. Hence, QLTI can expand and strengthen in areas other than its ocular business. Yet, there are at least two good reasons to do so in the field of NCBE. The first is the expertise and brand awareness that QLTI had built in this space. The second is to maximize synergy, efficiency, and scale effects along all levels of the value chain, and in particular, in discovery, development, and marketing. In general, diversification is a necessary means to reduce the risk inherent in the industry. A healthy pipeline, which consists of several products at different stages of development, stabilizes revenue stream.

An important tool at QLTI's disposal to attract collaboration with companies that have a NCBE product already at hand, is to utilize and further develop the technologies that become available to it as a result of its upcoming merger with Atrix. One such technology of Atrix is Atrigel®, which is a sustained release drug delivery system. The potential of a sustained release drug delivery to the ocular tissues is indeed promising. Such a system may provide a significant competitive advantage over the competing drugs of EYET and DNA, since it will significantly reduce the required number of injections into the eye. Repeated injections to the eye, the drug delivery method used by EYET and DNA, are uncomfortable to the patient, and likely to be associated with a higher rate of adverse events.

QLTI possess capabilities to expand its ocular franchise should it wish to do so. Specifically, it has the cash necessary for licensing activities and the expertise to evaluate their merit. Furthermore, licensing drugs at different stages of development would have a favourable effect its utilization of assets. For example, an immediate acquisition using some of QLTI's cash, and assuming unchanged Visudyne® sales, would lower the asset base, increase asset turnover, and increase ROA, ROI, and ROE. If debt is incurred, ROE will increase further. Over the long run, assuming revenues generated by sales of the new product, the ratios will go up even further.

By having a line of products in the NCBE space, QLTI's ocular business can better cope with industry forces, increase its leverage with buyers and suppliers, and perhaps even raise the entry barriers for new entrants, especially, if the potential hidden in the introduction to the NCBE market of a sustained release drug delivery materializes.

5.4 Raise QLTI's Brand Awareness

This is the third strategy to address the threat to the sustainability of QLTI's ocular franchise. Typically, biotech companies have less brand awareness than vertically integrated pharmaceutical firms, however, brand awareness is becoming increasingly important to QLTI's ocular business, as more choices are becoming available to the consumers (patients and doctors) in the near future.

It must be recognized that even within the constraints of QLTI's agreement with NVO, brand awareness can and should be created. Awareness can be raised without having a sales force, and without reference to a particular drug. For example, more than a year and a half prior to the expected launch of its product, Lucentis™, DNA, is already advertising at peer reviewed ophthalmic journals, in the following manner:

"...Bringing Biotechnology to Ophthalmology...."[48]

Similarly, DNA had a booth at the American Academy of Ophthalmology – the annual biggest Ophthalmology gathering - in October 2004.[49] QLTI must follow suit: it should adopt the same strategy. Importantly, the execution of a targeted campaign does not rely on a sales force. It could be executed by the small ocular marketing group at with the help of an external vendor. The decision to prioritize allocation of existing funds to this cause must be made at an executive level.

The ophthalmology market generally, and the market for NCBE in particular, is a niche market. As such, physicians' audience is relatively small and tightly linked, and can be easily targeted. Currently, QLT uses key opinion leader from the ophthalmic community to spread its gospel. However, presentations of papers and posters at Ocular conferences must be made by QLTI's own scientists, and in the company's name, relying on QLTI's core competencies in clinical research. In addition, a Fund for Young Scientists should be established by QLTI, in support of ophthalmic research, compounded by travel grants offered to these young scientists to attend ophthalmic conferences. Importantly, a global assistance program could be created, providing discounted drugs for uninsured patients.

All of the above initiatives will enhance QLTI's current brand awareness, and will create a brand equity pool from which QLT could draw in the future, when further ophthalmic drugs will be developed.

5.5 Give Higher Weight to Discovery Projects

Recognizing the segmentation in the biopharmaceutical industry and QLTI's position on the biotech side of the continuum, proactive action must be taken to prevent a drift toward no

[48] Ophthalmology, April 2004.
[49] American Academy of Ophthalmology 2004 Final Program Book

man's land, thereby, maintaining a competitive position. Change must occur at three planes: awareness, actions, and expectations.

At the awareness level, the high ratio between the number of chemical entities being investigated at the lab and at clinical trials should be mirrored at QLTI (Figure 1-1 Biopharma Research Stages). Hence, it must be recognized that the number of pre-clinical projects must far exceed the number of projects in development at any given time. Helping to sustain this ratio is the lower labour and capital toll of discovery projects. This ratio will keep the odds of innovation in favour of QLTI.

Specific actions must be taken to raise the quality of discovery. In principle, a commitment must be made to a dollar ratio between pre-clinical and clinical research. This will assist in attracting talent through a proactive process coordinated with HR. Recognizing that attention tends to be concentrated at the higher profile late stage clinical studies, an effort must be made to increase visibility of preclinical projects. Results must be presented and debated at internal meetings. Executives must show interest and appreciation of value created by attending the forums in which projects are discussed. Funds must be allocated to extend invitations to scientists for presentations at QLTI, and in turn QLTI scientists should be seconded to academic labs that are involved in research applicable to the projects QLTI is pursuing.

Finally, closing the circle, expectations from preclinical projects must be adjusted to conform to the preclinical norms. Measures of success must be adopted to recognize the knowledge gained by the organization through the experimentation process. Tolerance to generating results not readily applicable to development projects must be high.

A strong discovery is the long-term solution to a healthy portfolio. A balanced portfolio would affect the operating ratios in a similar manner to that of licensing activities. Ratios would increase due to sales of multiple products.

5.6 Summary

This chapter concludes the paper by providing recommendations that address issues which were brought up in chapter 4. Although the primary focus of this paper is QLTI's ocular business the recommendations, like the issues, have a broader scope. Drawing a surgical line between the ocular business at QLTI and rest of the company is difficult for several reasons. First, Visudyne® is QLTI's only commercial product and practically the sole source of its revenues. Second, Visudyne® related activities constitute a very significant proportion of the company's operations. Third, QLTI operates in a matrix structure, consequently, organizational competencies, or lack thereof, are reflected at the unit level.

Similar to the issues, recommendations are provided in decreasing order of urgency. As well, while the first set of recommendations applies exclusively to the existing Visudyne® franchise, the second set broadens the scope to an ocular franchise, and the final applies to QLTI as a whole. While the latter recommendation pushes the scope of this paper on the one hand, its implementation may have direct long term implications on the ocular business on the other.

The first set of recommendations addresses the threat posed by the new entrants to the NCBE market. It is suggested that the entry be considered as an opportunity to differentiate Visudyne® and to structure the industry for collaboration by treating the products as complementary and testing the hypothesis of an additive effect. The second set of recommendations is aimed at strengthening the sustainability of QLTI's ocular franchise. The first tier is expanding Visudyne's® life span; the second is expanding the portfolio to include other products in the NCBE field; and the third and final tier of the second set is raising brand awareness. The conclusive recommendation is to enhance overall discovery at QLTI overall as it is next to impossible to limit discovery according to therapeutic area. Finally, it is likely that with

these recommendations, especially as they relate to expanding the portfolio and discovery, the utilization of assets at QLTI would improve.

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