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October 1, 2018
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Dyadic International, Inc. (DYAI - OTCQX)

Trading At Cash; Billion Dollar Technology for Free

Based on our DCF model and a 15% discount rate, Dyadic International is valued at approximately $4.50 per share. We assume a 15% probability of ultimate success for C1, based on historical drug approval rates. The model assumes revenue contributions from sources worldwide.

Current Price (9/28/2018)	$1.69
Valuation	**$4.50**

INITIATION

Dyadic has developed a gene expression system based on C1, its proprietary fungal expression system that can produce a variety of recombinant proteins. C1 is already commercial in industrial applications and is in development for use in the development and production of pharmaceutical grade proteins. C1 exhibits potential to economically produce biologic vaccines, virus like particles, antibodies, Fc-fusion, enzymes and other biopharmaceuticals.

In 2015, the company sold its industrial business to DuPont for $75 million and retained the exclusive right to sublicense C1 for use in animal and human pharmaceutical applications. Proceeds from the DuPont sale provided cash for share repurchase and further development of the C1 platform for production of biologics. Additional R&D funding comes from partners. Dyadic is currently working with several biopharmaceutical companies and government organizations to validate the technology.

In the near term, we expect growing R&D revenue as additional partners are added. By 2020, we anticipate first sales-related revenues from C1, which represent licensing fees, upfront payments, milestones and royalties.

SUMMARY DATA

52-Week High	**1.73**
52-Week Low	**1.35**
One-Year Return (%)	**13.4**
Beta	**0.22**
Average Daily Volume (sh)	**45,591**
Shares Outstanding (mil)	**28.1**
Market Capitalization ($mil)	**47.5**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**10.8**
Insider Ownership (%)	**45.5**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2018 Estimate	**N/A**
P/E using 2019 Estimate	**N/A**
Zacks Rank	**N/A**

Risk Level	**Above Average**
Type of Stock	**Small-Growth**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue

(In millions of USD)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2017	$0.1 A	$0.2 A	$0.3 A	$0.2 A	$0.8 A
2018	$0.2 A	$0.2 A	$0.2 E	$0.2 E	$0.7 E
2019					$1.4 E
2020					$2.2 E

Earnings per Share

	Q1	Q2	Q3	Q4	Year
2017	$0.07 A	-$0.05 A	-$0.05 A	-$0.05 A	-$0.07 A
2018	-$0.07 A	-$0.06 A	-$0.07 E	-$0.06 E	-$0.26 E
2019					-$0.27 E
2020					-$0.30 E

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INITIATING COVERAGE

We are initiating coverage of Dyadic International Inc. (OTCQX: DYAI) with a $4.50 price target based on our estimates for commercialization of the company's proprietary C1 technology. C1 is a gene expression platform based on a fungus called *Myceliophthora thermophila*. The expression platform has generated commercial quantities of industrial enzymes used in energy production and is now being developed for use in production of biologic pharmaceuticals.

Dyadic is advancing the C1 platform to address a broad portfolio of biologic applications including vaccines, VLPs, monoclonal antibodies, enzymes, biosimilars and a new category called biobetters. C1 offers several advantages compared to the commonly used mammalian, viral and bacterial expression systems, such as Chinese Hamster Ovary (CHO), HEK-293, baculovirus and *E. coli*.

Exhibit I – C1 Pharmaceutical Applications



The advantages of C1 include its unique morphology that allows for greater yields, higher levels of purity for the expressed protein and a rapid development and production cycle compared to established protein secretion systems. Dyadic is enhancing the C1 platform to provide a safe and efficient gene expression system that will produce therapeutic proteins more quickly and at a lower cost compared to current production standards.

DuPont's purchase of the industrial rights to C1 was a vote of confidence for the technology. Dyadic has also developed multiple collaborations with two unnamed global pharmaceutical companies, Mitsubishi Tanabe Pharma, Sanofi-Aventis, ZAPI, and the Israel Institute for Biological Research, providing additional assurance that C1 is a legitimate expression system. Further evidence that this pursuit is relatively low risk is the R&D financial contribution made by partners. This allows Dyadic to maintain intellectual property rights to any improvements achieved in the system, while benefitting from capital contributed by others. Additionally, the company holds sufficient cash to fund its research and development internally and is not dependent on external financing.

Dyadic is currently working with partners to optimize C1 through maximizing yield, improving purity of output, and reducing the development and production cycle. The process also addresses glycosylation and protease deletion for efficacy and stability. Periodic updates have shown progress against these metrics.

Dyadic's C1 technology is differentiated from other expression systems in that it uses filamentous fungi as host for expression with several unique characteristics that allow for higher yield and greater purity than other mammalian, insect or bacterial systems. C1's attributes allow it to use lower cost media compared to other systems and eliminate purification steps due to the lack of viral contaminants. C1 has many attributes that may help it replace the current organization of expression systems.

We expect a steady pickup of research and license related revenues during the C1 development stage. Initial penetration will be modest as the C1 platform builds acceptance. While Dyadic may either sell the technology or be acquired, our valuation model assumes that the platform will be developed internally and receive development, license, upfront, milestone payments prior to commercialization of products through partners. Upon commercialization of products expressed by C1, milestones and royalties are expected.

There are a variety of factors supporting our thesis which argues for material penetration into the gene expression market. The increasing use of biologic drugs requires a revolutionary change that will impact end-user prices for broader acceptance. The C1 system can address both development and manufacturing costs, which are substantially higher for biologics than they are for small molecule drugs. C1's higher productivity and greater purity of output contribute to this advantage. The market for vaccines and monoclonal antibodies is estimated to be over $130 billion and over $200 billion for all biologics, with both growing at a double-digit rate. These statistics ignore additional targeted niches with difficult to produce proteins and the animal market. Even a modest penetration into mAbs, vaccines and VLPs provides a dramatic revaluation upward from current levels.

INVESTMENT THESIS

There are several protein expression systems employed today including mammalian, bacterial, insect and fungal that are used to produce biologic drugs. The most common system is the Chinese Hamster Ovary (CHO) cell line due to industry familiarity and mammalian post-translational modifications. Despite the benefits and dominance of this cell line, CHO and other common systems appear to have reached a limit in terms of yield, rapidity of protein expression and consistency of output and purity. With the large and growing demand for biologics and high costs for end consumers, there is a need for greater yield and purity for recombinant proteins and lower capital intensity. Revenues from protein expression, including vaccines, monoclonal antibodies and biosimilars, exceeded $130 billion in 2017 and are expected to grow at a 10% CAGR until 2025. With limitations on current production capacity and long fermentation times using the CHO platform, a revolutionary alternative is needed.

Prices for new biologics seem to reach new highs every few months. Examples such as checkpoint inhibitors go for about $150 thousand per course of treatment, and orphans such as Alexion's Soliris comes in at over $400 thousand per year. To address the high costs of biologics, two factors need to be in place: greater competition and lower manufacturing costs. There is an intense search to find a solution along this dual axis and C1 may provide it.

C1 is a modified strain of the fungus *Myceliophthora thermophila* which has evolved to produce proteins from a dramatically smaller form factor than its ancestor. It is a filamentous fungi that has evolved into shorter and shorter filaments while improving its protein secretion rate. It also has competitive levels of productivty that have not yet been optimized and has already exceed CHO productivity levels using a simpler and lower cost media.

CHO cell production rates have been relatively flat for over a decade which suggests future volume growth will be directly tied to net increases in newbuild capacity under the present system. With demand increases for vaccines, mAbs and other proteins expected to grow double digits over the next decade, new production methods are needed that have substantially higher productivity. The combination of new expression cell lines and single use bioreactors (SUBs) may be able to address this demand without the need for a substantial increase in fixed capital investment. Dyadic is working with its contract research organizations to improve C1 technology to produce higher yields at a lower cost with greater accuracy and purity of output.

We anticipate that revenues in the near term will consist of research funding, license fees, upfront payments and milestones from partners developing C1 for use with their biologics development programs. Drug development programs can last up to a decade or more before regulatory approval is granted. Therefore, we anticipate royalty revenues to be received after a development period with steadily increasing penetration as the system is validated. Our target price is generated based on penetration into the broad recombinant protein market and value added by C1 to upstream manufacturing. There are other applications and cost reduction opportunities that may also be developed which will be added to our forecasts as they become more certain.

Key reasons to own Dyadic shares:

- **High cost of biologics production demands lower cost alternative**
- **C1 technology provides faster cell line development and production cycle**
    - **Technology addresses high cost component of drug manufacture**
    - **Favorable characteristics of productivity and purity**
    - **Less stringent operating conditions required**
    - **Low-cost synthetic growth media used**
    - **Avoids mammalian cell related viruses, reducing purification steps**
    - **Particularly beneficial for expensive, difficult to produce recombinant proteins**
- **Natural alignment between C1 and biosimilars/biobetters due to cost focus**
- **Development fully funded with cash on the balance sheet and partner contributions**
- **CEO holds dominant share of business and has history of cost conscious development**

Based on our DCF valuation model, which assumes a royalty based on savings C1 can provide to the industry, we initiate Dyadic International at $4.50 per share.

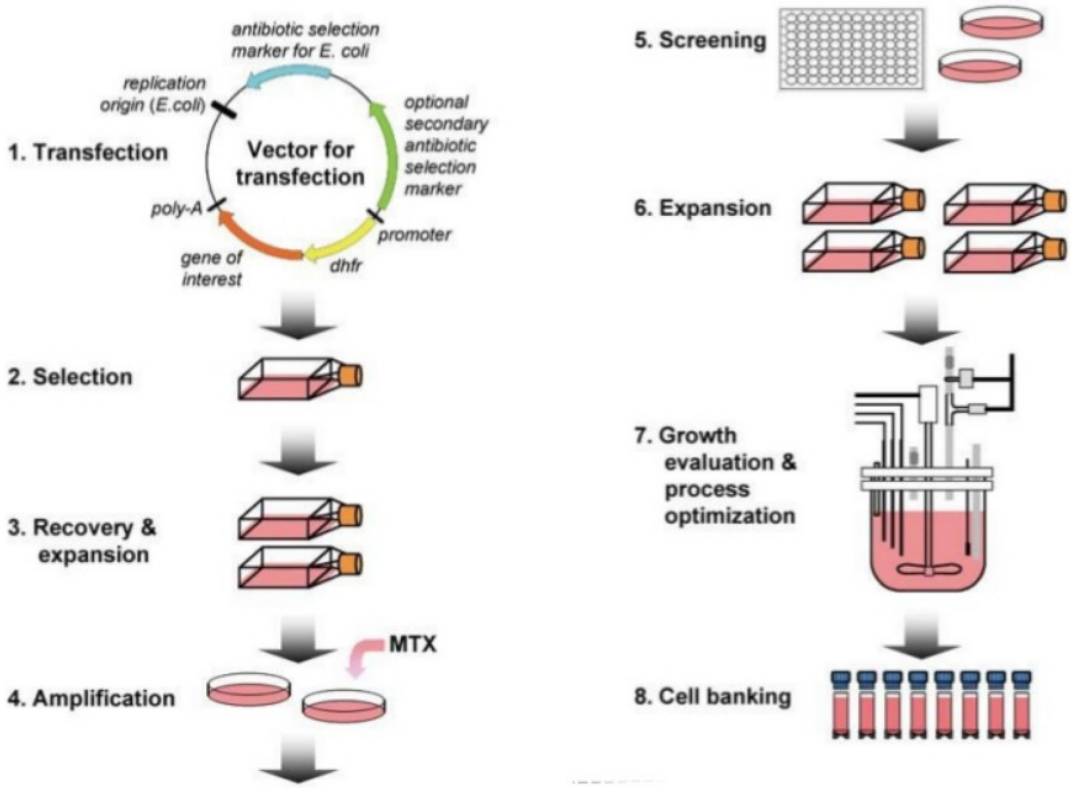
Therapeutic Protein Manufacturing

In 1976 Genentech expressed the first recombinant protein in *Escherichia coli* (*E. coli*), producing Somatostatin, a growth hormone inhibitor. 1978 saw the first human insulin prepared with recombinant DNA, also using *E. coli*, launching the pharmaceutical world into the age of therapeutic protein manufacturing. Other expression systems were subsequently developed, such as insect, yeast and mammalian approaches, providing the mechanism for more complex protein production. Since the 1980s, when the first human recombinant enzyme Alteplase was manufactured in Chinese hamster ovary (CHO) cells, the biologics manufacturing world preferred the use of CHO cells for human use biologics. CHO was favored in the expression of proteins due to its ability to grow in large scale production, reproduce across multiple batches with better safety, generate higher yields and provide post-translational modifications. The system has been integrated into the manufacturing world and is well understood by regulatory authorities despite drawbacks related to costs, efficiencies and output quality. Current expression systems produce therapeutic products including monoclonal antibodies (mAbs), vaccines, tissues, cytokines, enzymes, fusion proteins, whole cells, bi-specific antibodies and viral and nonviral gene therapies.

The process for producing a desired protien requires several specific steps that begins with selecting a host production organism and navigating the upstream and downstream efforts that generate a product suitable for human use.

The upstream process[1] for generating recombinant proteins is responsible for cell expansion, and growing selected cells into larger and larger volumes until they reach the bioreactor where the targeted protein is expressed. The first step in the process is transfection, which can be achieved through a variety of methods such as lipid nanoparticle, electroporation, retroviral-mediated processes and others. After DNA has been delivered, cells with successful integration of the vector will express the target protein and are retained. Cells that did not successfully integrate the target instructions are discarded during the selection process and desired cells are recovered and expanded. The next step is the amplificaion stage where remaining cells are exposed to high levels of methotrexate which isolates high expressing cells.

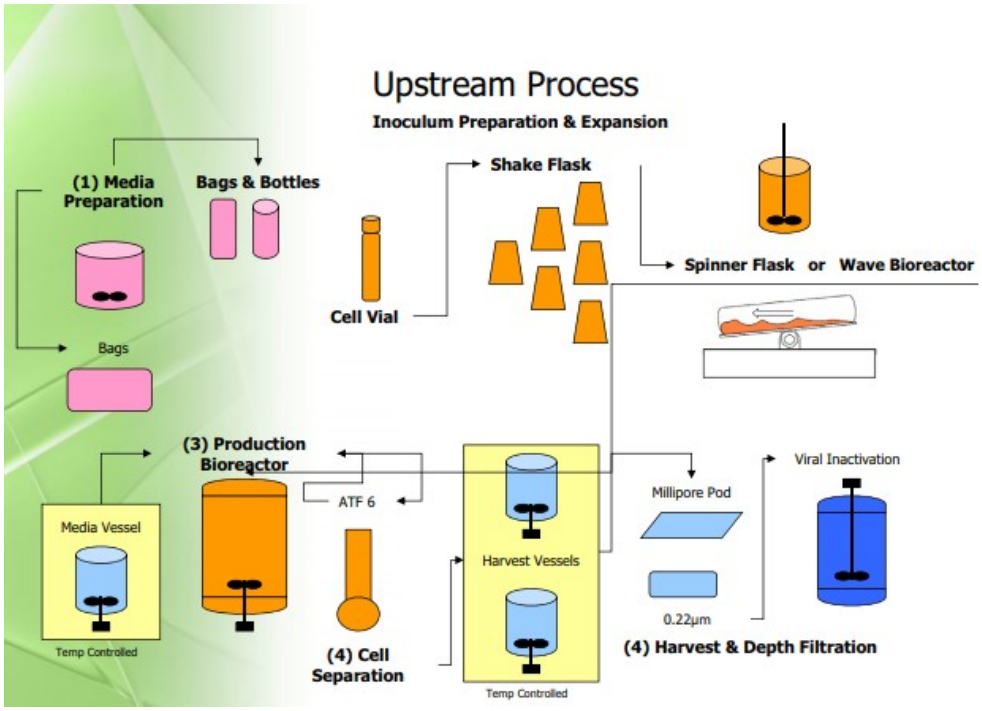
Exhibit II – Cell Line Development[2]



[1] https://www.thermofisher.com/us/en/home/life-science/protein-biology/protein-biology-learning-center/protein-biology-resource-library/pierce-protein-methods/overview-protein-expression-systems.html
[2] Jayapal, KP, et al. Chemical Engineering Progress 103.10 (2007): 40.

Following amplification, which selects cells with high productivity, there is a pool of heterogenous cells with varying output quality. During screening, individual clones with the highest individual productivity and growth rates are segregated. This is achieved by a series of limiting dilutions in multi-well plates to separate colonies with uniform cell populations. From 10% to 30% of the well-plate population is selected for candidate cell lines. The selected clones are disseminated through several rounds of subculturing in fresh media to facilitate further expansion. The expansion generates the desired clones which are evaluated in bioreactors to simulate a mass production environment. After evaluation, a cell line is chosen which is used to produce the target protein for use in clinical trials and later in mass commercial production. There are also additional steps that introduce post-translational modifications such as glycosylation which impact the biologic activity of the drug.

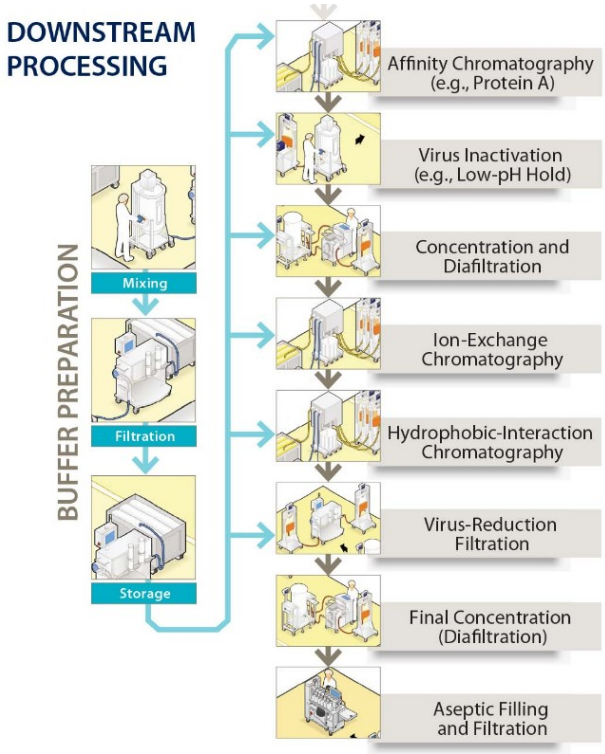
Exhibit III – Upstream Biomanufacturing Process[3]



After the preparation of the final, formulated drug substance, downstream processing takes place. Downstream work predominantly focuses on yield and purity and removes viruses, bacteria, reagents, toxins and other host cell components. The removal process for monoclonal antibodies typically requires Protein A chromatography, concentration (through evaporation), diafiltration of salts and solvents, multiple types of other chromatography and filtration. Purification may also be accomplished by chemical inactivation, centrifugation, sedimentation, and extraction among other methods. Most bioprocessors cite downstream processing as the production bottleneck with chromatography as the key hurdle.[4] Protein manufacturing encompasses a wide variety of biologic products. Each has its own specific processes, but they all roughly follow the upstream and downstream steps explained herein.

[3] Cytovance Biologics Inc., John Conner, 2013
[4] http://www.pharmtech.com/top-trends-biopharmaceutical-manufacturing-2017-0

Exhibit IV - A generic downstream process flow diagram for a monoclonal antibody[5]



Competing Recombinant Protein Expression Systems

The vast majority of protein manufacture for human use is performed by CHO cells, which were first used for cell line development in the 1950s. There are also other popular expression vectors which include fungal, insect, bacterial and yeast (which is a fungal system subtype). The selection of a specific expression system relies on the post-translational modifications (PTMs) desired and other factors including cost, productivity and time to production.

Mammalian systems such as CHO frequently use plasmid transfection and viral vector infection to introduce the instructions for protein creation. This process takes several weeks to months to create a stable cell line and the viral vector can be transfected in a few days. There are a few types of expression systems including transient, for research use and stable, which is applicable for generating biologics-grade product. Stable expression allows the foreign DNA to replicate for an extended duration in the host cell but also requires an extended process to create. The main benefit of the mammalian system is the quality of the PTMs for protein initiation signals, processing, secretion and glycosylation. The PTMs generate higher rates of activity and provoke immunogenicity.

Yeast systems have been used for thousands of years in beer and bread production and now in the field of genetic engineering. Common use has led to their classification as GRAS (generally recognized as safe) by the FDA, with no production of toxins, reducing safety concerns and costs. This class may not be as suitable for high-density culture as it has low secretion efficiency, especially for large molecular weight proteins. There are a variety of yeast cells which can be used, and they vary in their PTMs, which makes selection of the proper host critical to the specific application needed.

Insect systems use the Baculovirus insect virus to insert the gene of interest into the cell. Baculoviruses are double stranded DNA viruses that naturally infect host insect cells and are able to express recombinant proteins. The system produces PTMs including proteolytic processing, phosphorylation and glycosylation, despite the glycosylation pattern not being a precise match for mammalian cells. High levels of expression and inherent safety during manufacture are other key benefits. The Baculovirus system can accommodate large inserts, which allows for the delivery of multiple genes. However, it does have some drawbacks including the time required for growth of the initial cell line (10 – 12 days) and cell culture is only sustainable for a few days. Additionally, compared to yeast systems, set up time is consuming. Baculovirus has been used to produce alpha and beta interferon, erythropoietin, interleukin 2 and others.

[5] Bird, P.; Hutchinson, N.; Automation of a Single-Use Final Bulk Filtration Step: Enhancing Operational Flexibility and Facilitating Compliant, Right–First-Time Manufacturing. March 10, 2015. http://www.bioprocessintl.com/wp-content/uploads/2015/03/13-3-sup-Bird-F1.jpg

Bacterial systems predominantly use *E. coli* as the host cell, employing a plasmid vector to insert the proper DNA fragment. *E. coli's* genetics are well known and the host is used broadly for the production of heterologous proteins, and is a less complex system than yeast, insect or mammalian cells. While it is simple and inexpensive to use, there are some disadvantages. Some of the difficulties in using bacterial systems include aggregation problems under high levels of overexpression and the lack of PTMs. The lack of sufficient PTMs, including protein glycosylation make it inappropriate for most human biologics use.

Exhibit V – Recombinant Protein Expression Systems

Class	Example	Strengths	Weaknesses	Products
Mammalian	CHO, HEK293	Expression is easy & rapid, provides post-translational modifications; stable transfection produces higher yield, scalability & reproducible production	Suspension cultures required, costly culture conditions; reduced efficiency & levels of protein expressed	mAb, high PTM requirement
Yeast*	*Pichia pastoris*, *S. cerevisiae*, *K. lactis*	Cost Effective, simple media, rapid expression	Lacks mammalian glycan structures	mAb, enzymes
Insect/ Viral	Baculovirus	Provides eukaryotic protein processing, favorable solubility, provides majority of post-translational modifications of mammalian cells	Glycans do not match typical mammalian structures; expensive; difficult to scale; viral contamination	Membrane proteins, β interferon
Bacterial	*E. coli*	rapid proliferation, high expression, easy purification, good stability and low cost	Lacks post-translational modifications; toxic pyrogens; proteins not properly folded	Small proteins
Fungal	C1, *Aspergillus niger*	Rapid expression, low cost media	Glycosylation, proteases	Broad variety

Chinese Hamster Ovary (CHO) Production

While CHO production is the workhorse of the protein expression world, the system has drawbacks. Some critics see conventional mammalian cell lines as insufficient to produce bi-specific and tri-specific and other advanced biologic molecules. There are long lead times for development of stable and accurate cell lines and yields appear to have plateaued.

In 1957, Dr. Theodore Puck, who was a geneticist at the University of Colorado, isolated ovary cells from a female Chinese hamster to develop a cell line that provided fast generation times of culture *in vitro*. Since then, CHO cells have been used to produce recombinant therapeutics and biopharmaceutical production.[6] They have emerged as the dominant host for production due to their resiliency, fast generation times, adaptability to a variety of cultures, relatively low risk of viral propagation and ease of use in experiments.[7] CHO provides important product features, such as protein folding and post-translational modifications and are able to grow in suspension, allowing the use of large, stirred-tank bioreactors. The cells are amenable to genetic modifications that permit the introduction of exogenous DNA and the resulting protein expression. CHO cells also produce glycoforms that are closely aligned with human biology.

These favorable characteristics led to over $140 billion[8] of CHO cell production in 2014 and its use in over 70% of approved recombinant proteins.[9] Many of the best-selling biologics use these CHO for expression including Humira, Rituxan, Avastin, Herceptin and Enbrel[10] resulting in all stakeholders gaining intimate familiarity and comfort with the system.

Despite the benefits listed above and their widespread use, CHO cell production presents several difficulties. Due to limited production capacity, construction and maintenance of large, capital-intensive production facilities are required to produce sufficient quantities of desired recombinant proteins. The majority of Chinese Hamster Ovary cell yields fall within the 1 – 5 g/l/d range and are realized over a cell culture duration of 10 – 14 days.

[6] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5152558/
[7] Dumont, K; et al.; Human cell lines for biopharmaceutical manufacturing: history, status, and future perspectives. Crit Rev Biotechnol. 2016 Nov 1; 36(6): 1110–1122. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5152558/
[8] Walsh, G. Biopharmaceutical Benchmarks 2014. Nature Biotechnology Volume 32, Issue 10, 1 October 2014, Pages 992-1000.
[9] Dumont, K; et al.; Human cell lines for biopharmaceutical manufacturing: history, status, and future perspectives. Crit Rev Biotechnol. 2016 Nov 1; 36(6): 1110–1122.
[10] https://www.pharmasalmanac.com/articles/cell-line-development-for-therapeutic-recombinant-proteins

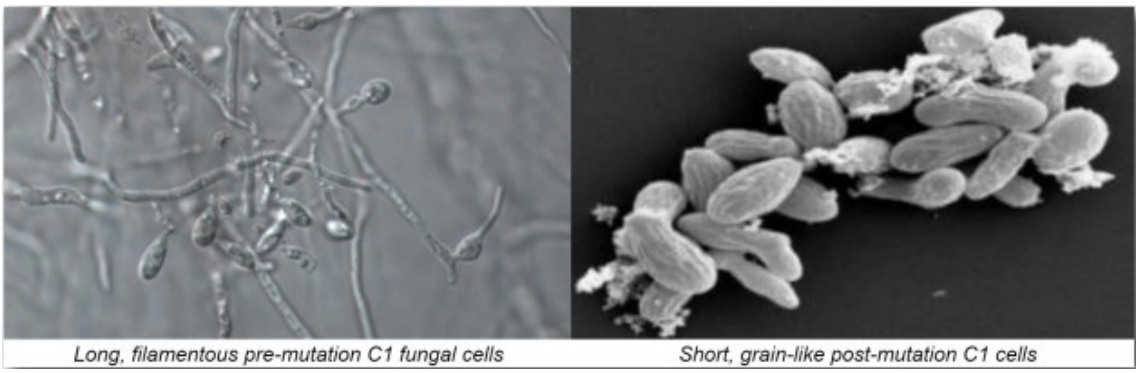
Some of the other shortcomings of CHO systems include:

- PTMs are not consistent with human proteins
- Post-translational N-glycans can negatively affect the biologic activity, protein stability, clearance rate and immunogenicity of biotherapeutic proteins
- Expensive media
- Viral contamination
- Off-target protein production

Development of C1

C1, a modified strain of *Myceliophthora thermophila,* is a fungus that has been engineered over time and was originally isolated from alkaline soil in forests of eastern Russia to act as a secretor of natural cellulase. On behalf of Dyadic, Russian scientists isolated it in the 1990s to produce cellulase enzymes used to manufacture distressed denim in the apparel industry. The scientists were able to enhance the production of cellulase from C1 by exposing the fungal cells to ultraviolet light, which provoked a beneficial mutation. This transformation let to a reduction in size of the filaments from long strands to short, which produced a greater number of secreting ends per unit of length resulting in higher productivity. The change in morphology of the C1 fungus also reduced the viscosity of the cells in solution, which allows it to express proteins in large tanks. The greater fluidity of the modified fungus also allowed it to be used in microtiter plates enhancing the testing and expansion process.

Exhibit VI – Comparison of Pre and Post Mutation C1



Long, filamentous pre-mutation C1 fungal cells *Short, grain-like post-mutation C1 cells*

C1 has a number of characteristics that are favorable as a potential alternative protein expression system. The fungus has a unique morphology that has been used in industrial production of enzymes for more than 20 years producing commercial enzymes in 500,000 liter bioreactors. It also exhibits high productivity, is able to use low cost media for fermentation, expresses at high purity and allows for fewer purification steps which reduces costs. The C1 system also allows for a wider range of pH and temperature to be used as compared to CHO and other systems. This flexibility can limit the impact of proteases, modify glycosylation and have other beneficial impacts. C1 demonstrates a much faster fermentation cycle time of four to seven days, which is about half to a third of the CHO standard of 10 to 14 days. It is likely that the output peak for C1 has not yet been reached and the potential productivity could be greater than pre-commercialization levels.

Dyadic can pursue multiple products with C1 including recombinant vacines, virus like particles (VLPs), new biologic therapies, and biosimilars (biobetters) that are either glycosylated or non-glycosylated. In addition to expressing biologics at the same or improved quality as the innovator, the system can also produce at a much more efficient level generating higher yielding gene expression for biomanufacturing. Greater efficiency will allow some previously non-economic protiens, such as certain bi-specific antibodies and VLPs to be commercialized. Dyadic anticipates that its R&D activities will improve C1 to a level where it can function as a favored alternative to CHO, *E.coli* and other expression systems for a variety of biologics products.

Since December 2015, Dyadic has been focused on the development of their protein expression platform and has successfully achieved several milestones, including progress on protease deletion, glycosylation and productive capacity. Through their efforts with their contract research collaborators VTT and BDI, Dyadic has generated initial data showing C1's ability to express a wide variety of recombinant proteins.

Exhibit VII – C1 Portfolio of Expressed Recombinant Proteins

Monoclonal Antibodies (mAbs)	Fab antibody fragments	Fc-Fusion proteins
Virus Like Particles (VLPs)	Bi-specific antibodies	Antigens

Full-length mAbs have been produced at 2.4 g/l/d and Fc-fusion proteins at 1.35 g/l/d. mAb binding properties were similar to CHO-produced control mAbs. Dyadic announced in September a certolizumab yield of 2.0 g/l/d and a VLP yield of 300 mg per liter. As optimal conditions and promoters are applied, we expect continued improvement.

Additional work has been performed to demonstrate that the binding kinetics of C1's mAbs match those of approved mAbs produced from CHO cells. An experiment was run using a commercially available ligand produced in CHO which was compared against a C1 produced mAb. A Biacore T200 assay was used to measure the binding properties of the mAbs to the ligand, which generated data demonstrating virtually identical binding kinetics.[11]

Interest by biopharmaceutical companies has been intense and over 100 confidential disclosure agreements to start collaborations have been signed. The company is also conducting outreach to potential research and business partners, and governmental agencies and currently has four funded feasibility and expression projects and has completed two funded proof of concept collaborations with large pharmaceutical companies.

Using current production systems, it can take from 14 to 18 weeks to advance from transfection to bioreactor due to the slower expression rate of popular expression systems. C1 is able to develop cell lines in 10 to 14 weeks saving 30% to 40% of the time required in the upstream process. Fermentation lasts 10 to 14 days using standard production systems, while C1 is able to achieve this in a 4 to 7 day cycle.

Filamentous fungi are naturally prolific hosts for endogenous proteins and are widely used in the production of enzymes for biofuels, food, textile, paper and chemical industries. The differentiating characteristics of fungal systems are their natural capacity to secrete high levels of enzymes and provide faster, less costly fermentation using lower cost of media. There are several attributes of C1 compared to CHO where it has a much faster rate of reproduction and a cost or efficiency advantage.

Why Must We Find More Efficient Protein Expression?

Cost and speed. In 2013, an article noted that biologics treatments cost about 22 times more than small molecule treatments[12] and can generate profit margins of up to 40%. That same year, Express Scripts highlighted the rising spend on specialty medications, pointing out that only 2% of people in the U.S. use biologic drugs, yet they account for 40% of prescription drug spending.[13] This statistic was reiterated by current FDA commissioner Scott Gottlieb[14] in a recent statement arguing for a more efficient development process for biosimilars. With pharmaceutical costs already at unaffordable levels, an opportunity to dramatically reduce production costs merits attention.

Exhibit VIII – Brand Name Drug Price Inflation[15]



[11] Dyadic July 2018 Corporate Presentation, Slide 17. https://www.dyadic.com/wp-content/uploads/2018/01/C1-Update-Presentation-July-23-2018.pdf
[12] Blackstone, Erwin; Joseph, P.F.. The Economics of Biosimilars. Am Health Drug Benefits. 2013 Sep-Oct; 6(8): 469–478.
[13] http://lab.express-scripts.com/lab/insights/industry-updates/the-$250-billion-potential-of-biosimilars
[14] https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm613881.htm
[15] https://www.aarp.org/content/dam/aarp/ppi/2016-12/trends-in-retail-prices-dec-2016.pdf

A few factors are behind these price increases. Some of the rise is attributable to the strong negotiating position of biopharmaceutical companies. Other factors include less competition from biosimilars, longer exclusivity periods for biologics and a difficult pathway for biosimilar approval which has led to a relatively higher inflation rate for this class. Another important component is attributable to cost.

One of the efforts made to combat soaring drug prices was the Biologics Price Competition and Innovation Act, which created a shortened approval pathway for biosimilars. Despite the good intentions, the cost and difficulty of pursuing a biosimilar has limited the number of new candidates pursuing this route. A 2013 journal article found that the average daily cost of a biologic drug was $45 as compared to $2 for a chemical drug.[16] This ratio has only increased over the last five years due to price inflation in biologics.

A NY Times[17] article noted that the largest revenue biologic on the market, Humira, costs $38,000 per year after rebates. The article also raised the issue of the high costs of biologics since they are "made from living cells rather than synthetic chemicals."[18] According to research conducted by Pfizer,[19] a successful biosimilar can take from five to nine years to develop and over $100 million to fund the analytical, nonclinical, PK/PD and clinical studies process. This compares to the $2.6 billion and 10+ years for a new medicine, which includes the cost of failures.

Biologics development cost is dramatically higher than small molecule development cost due to the complex development of cell lines, manufacturing in bioreactors and purification. In addition to the many processing steps, it can take months to go from an identified product to output ready for use. A more efficient expression system can help reduce complexity, development costs and time commitment. Currently the lowest costs come from the largest bioreactors, which are 10,000 liter stainless steel vessels that reside in South Korea,[20] estimated to produce at $100 per gram; however, it is unclear if this includes appropriately allocated capital costs, which are substantial and this also assumes that full capacity of the reactors is used. Smaller reactors, in the 2,000 liter range can produce for $175 to $225 per gram.[21,22] Outside of the most competitive facilities, costs range from $500 to $1,000 per gram for fixed production equipment.

Process innovation lags product innovation; however, when a product class is better established and there are more pressures on price, then there is a focus on process changes. There are certain classes of proteins that are difficult to express in sufficient volume, such as Fc-proteins. Low yield and long timelines preclude them from being pursued commercially. With a more efficient production host, they may become economically feasible, thereby expanding the selection of recombinant proteins available.
The needs of a more economic expression system include:[23]

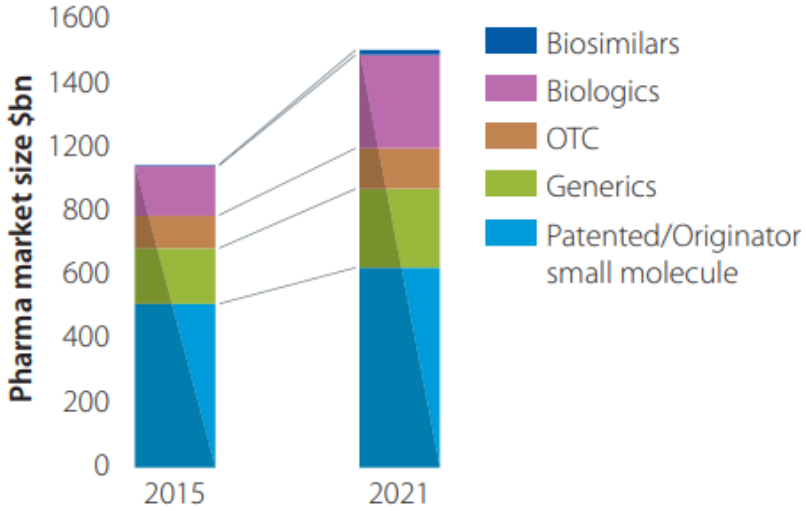
- Rapid doubling time
- Higher yields
- Ability to grow in simple and inexpensive media
- Compatibility with linear scale-up
- Simplicity in purification
- Molecular structure as closely matching the natural protein

Cost Pressures Mandating Change

The monetary value of the global pharmaceutical market is over $1 trillion per year and the vast majority of revenues are derived from small molecule drugs and their generic descendants. However, biologics have become an important part of the landscape with revenues of approximately $200 billion in 2017[24] and they represent the fastest growing segment. As this market becomes a larger part of healthcare spending, it is likely that declining affordability will hamper growth and the ability to treat patients without a fundamental change in the cost and competition structure.

[16] Blackstone, Erwin; Joseph, PF. The Economics of Biosimilars. Am Health Drug Benefits. 2013 Sep-Oct; 6(8): 469–478.
[17] https://www.nytimes.com/2018/01/06/business/humira-drug-prices.html
[18] https://www.nytimes.com/2018/01/06/business/humira-drug-prices.html
[19] https://www.pfizerbiosimilars.com/biosimilars-development
[20] https://www.pharmamanufacturing.com/articles/2016/manufacturing-costs-will-be-critical-to-biosimilars-success/
[21] https://www.pharmamanufacturing.com/articles/2016/manufacturing-costs-will-be-critical-to-biosimilars-success/?show=all
[22] This includes both upstream and downstream costs
[23] Legastelois, Isabelle, et al. Non-conventional expression systems for the production of vaccine proteins and immunotherapeutic molecules. Hum Vaccin Immunother. 2017 Apr; 13(4): 947–961. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5404623/
[24] Biologics Global Market Report

Exhibit IX – Pharmaceutical Market Segments 2015 and 2021 Sales Estimate[25]



One common theme we address in our research is the inflationary cost pressures present throughout the pharmaceutical value chain. Prescription medication is approximately 10% of total health care costs[26] and represented $325 billion in 2017.[27,28] This equates to almost $1,000 for every American every year[29] and over $11,000 per year for those over 65. Pricing for specialty drugs, which includes biologics, increased approximately 9% per year every year from 2010 to 2015.[30,31]

A GAO report found that much of the rise in drug spending was driven by the use of brand name drugs and over the period of 2010 to 2017, the increase in the price of patented drugs rose an average of 18% every year.[32] Branded drugs with no generic alternatives have increased even more, rising at a 25% average annual rate.[33] These statistics illustrate the high and increasing prices for pharmaceuticals which are not sustainable in the long term. We see change as inevitable either through a radical revolution in the private health care system or government action. When this occurs, manufacturers that have anticipated the realignment with affordability will have already shifted towards lower cost structures and those that have not yet changed will quickly do so. In the world of biologics, a material component of cost that will be addressed for both development and production is the efficiency of the protein expression system.

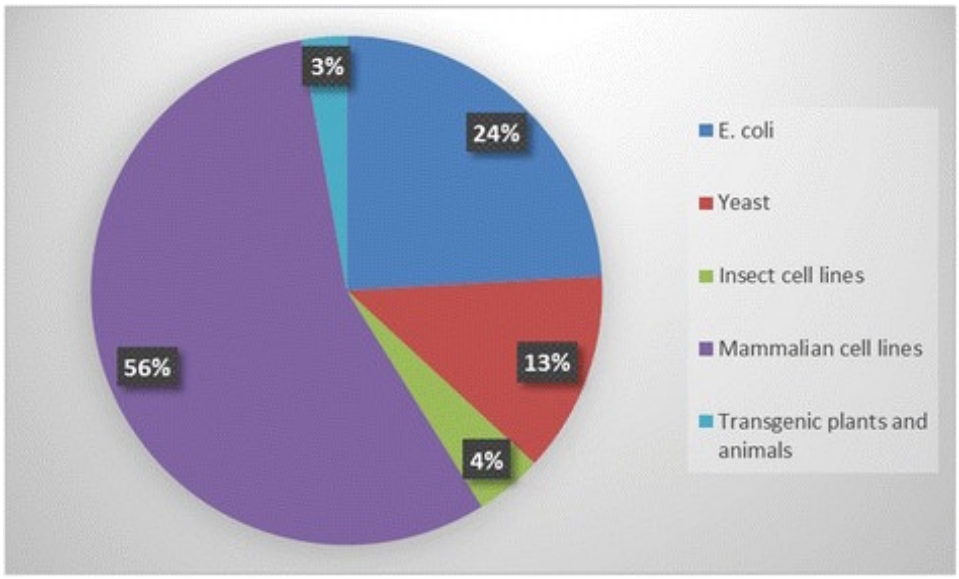
In the new paradigm, many areas of health care must become more efficient. Research and development, the regulatory process, marketing and distribution, production and other cost centers will tighten their belts to make critical medicines affordable. In contrast to small-molecule drugs, biologics have relatively high production costs due to the complex manufacturing process, making this a focus area.

Production Cost Analysis

We have performed an exhaustive review of industry and academic articles and reports to determine a range of costs for upstream activities. Most producers limit public disclosure of their operating costs for competitive reasons; however, there are industry specialists that have compiled surveys and applied theoretical parameters and outputs to generate production cost estimates. Costs vary among protein types, with vaccines on the low end of the cost spectrum, mAbs in the middle and complex proteins that require extensive post-translational modifications on the high end. For simplicity, we will focus on mAb production in mammalian expression systems as it comprises over half of total production, is not on either extreme in terms of cost, and data exists to generate an estimate.

[25] Pharma & Biotech 2017. Review of Outsourced Manufacturing.
[26] Kaiser Family Foundation analysis of National Health Expenditure (NHE) Historical (1960-2016) and Projected (2017-2026) data from Centers for Medicare and Medicaid Services, Office of the Actuary, National Health Statistics Group (Accessed on May 2, 2018)
[27] IQVIA National Sales Perspectives, IQVIA Institute, December 2017. https://www.iqvia.com/institute/reports/medicine-use-and-spending-in-the-us-review-of-2017-outlook-to-2022
[28] Total health care costs are $3.3 trillion and 18% of gross domestic product. From Centers for Medicare & Medicaid Services, 2016 Data. https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/NationalHealthAccountsHistorical.html
[29] Calculated based on OECD data here: https://data.oecd.org/healthres/health-spending.htm#indicator-chart
[30] AARP Rx Price Watch Report. Trends in Retail Prices of Specialty Prescription Drugs Widely Used by Older Americans, 2006 to 2015. September 2017.
[31] In 2010 the average annual price of specialty drugs was $27,182 and increased to $52,486 in 2015.
[32] http://www.modernhealthcare.com/article/20171228/NEWS/171229930
[33] http://www.modernhealthcare.com/article/20170504/NEWS/170509935

Exhibit X – CHO & Mammalian Output Comprise the Majority of Biologic Production[34]



Production cost varies widely with volumes produced. For the largest stainless steel bioreactor manufacturers that are producing at full capacity, upstream and downstream costs can fall to $100 per gram. For smaller operations, that are running a variety of batches of product and are not able to attain the efficiencies of scale, costs can rise to $1000 per gram. Our review found that costs of approximately $500 per gram and below were competitive for most commercialized products. Smaller volume products, orphan drugs and products in development have much higher unit production costs.

Approximately 40% of production costs are upstream[35] and 60% downstream. C1 can benefit both ends of the production continuum due to its faster expression ability, lower upstream media costs and cleaner, more consistent output for downstream benefits. Our analysis will focus on the upstream portion as we are better able to quantify the cost savings. Based on the 40% breakdown, competitive upstream costs for mammalian systems are from $40 to $200[36] for commercialized product and $500+ for lower volume and difficult to produce products.[37] Other research we reviewed found upstream processing costs from $32 to $100 per gram for mAbs;[38] however, this may be understated due to the exclusion of inefficiencies, such as product changeovers, that would lower utilization.

Media costs range widely, from about $2 per gram up to $14 per gram;[39] however, we see the competitive bounds from $2 to $7 per gram with an average cost of $5.

Based on our review, we estimate an average cost of $100 per gram for the most efficient manufacturing, with $5 of this total allocable to media costs. C1 has demonstrated that it is able to produce an average of 2.4 g/l/d compared to competitive CHO production rates of 0.4 g/l/d or a 6:1 ratio. C1 can express other proteins at a similar or more favorable ratio. C1 media cost is estimated to be about €0.23 per gram of production or about $0.28. This is a reduction in cost by a factor of 18 (0.0556x). Due to the small contribution from media and to maintain a conservative approach, we assume that the cost to produce a gram of recombinant protein using C1 (including media) is 1/6 the cost of using the common mammalian systems widely used. Therefore, by using C1, the cost of producing a gram of recombinant protein falls from $100 to about $17 ($83 savings per gram). This is only the average for the most efficient plants, and the benefit for difficult to produce and low volume recombinant protein is greater. At $200 per gram in upstream costs, using the C1 system saves $167 per gram and at $400 per gram, the savings expand to $333 per gram. C1 can even expand the market to include previously cost prohibitive products due to its more efficient productive capacity.

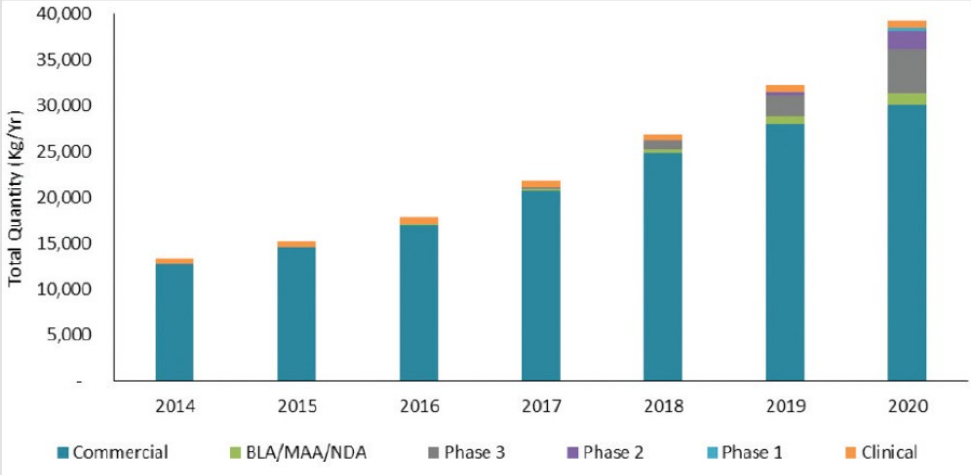
C1, due to its high purity of output and the lack of mammalian viral contaminants can skip two downstream purification steps. We lack sufficient data to reasonably estimate the cost savings and modifications required; therefore, we will update the downstream benefits when more information becomes available.

[34] Baeshen, Nabih; et al. Cell factories for insulin production. Microb Cell Fact. 2014; 13: 141. Published online 2014 Oct 2.
[35] Latham, Peter; et al. Costing Issues in the Production of Biopharmaceuticals. February 1, 2004.
[36] Mab manufacturing today and tomorrow – Reducing risk, reducing cost. Biopharm Services Limited, 2014.
[37] Rader, Ronald. Manufacturing Costs Will Be Critical to Biosimilars' Success. BioPlan Associates. 2017.
[38] Mab manufacturing today and tomorrow – Reducing risk, reducing cost. Biopharm Services Limited, 2014.
[39] Kelley, B. Industrialization of mAb production technology: The bioprocessing industry at a crossroads. MAbs. 2009 Sep-Oct; 1(5): 443–452.

Production Volumes

Current volume for mammalian protein manufacture is estimated to be from 20,000 to 25,000 kilograms per year. This forecast was developed by taking volumes used by patients treated in the most recent year data was available and growing in line with sales estimates, backing out price increases. See the graphical representation below.

Exhibit XI– Forecast of Bulk Kilograms of Mammalian Protein Production[40]



Flexibility Benefits of Single Use Bioreactors

Single use manufacturing is able to avoid the majority of capital costs and long lead times associated with the large stainless steel bioreactors. It offers additional flexibility, faster turnaround and is adaptable to any size production. In a review with company managements, consultant BioPlan Associates found that having a manufacturing facility optimized for maximum capacity utilization was the most important factor in cost competitiveness. A flexible plant will be able to bring effective capacity to about 85%.[41] Capital costs for new facilities range from $200 to $500 million[42] and a new Samsung Biologics plant in South Korea is estimated to cost $740 million,[43] all of which must be allocated to future production. These plants can also take up to three years to build.[44]

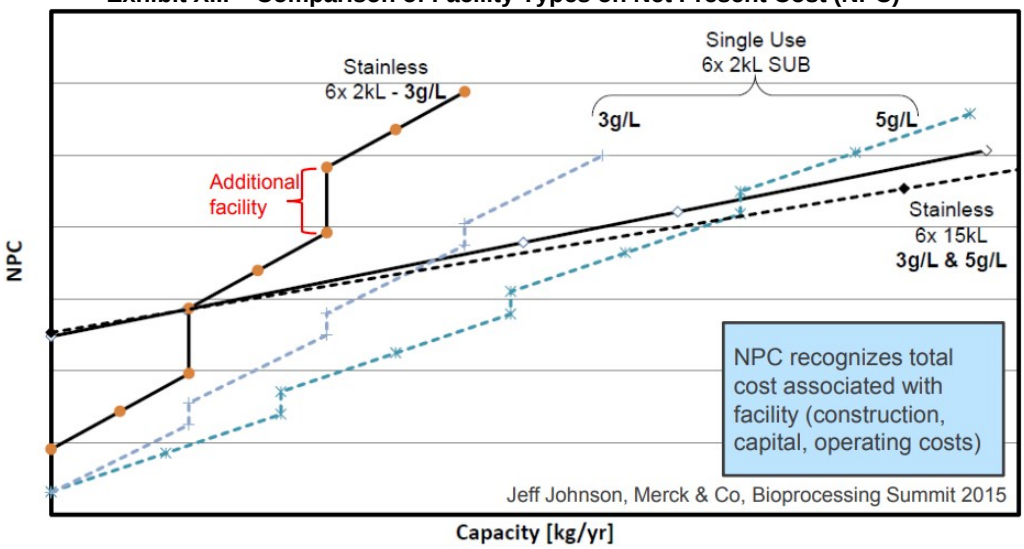
Exhibit XII – Single Use Bioreactor



[40] Seymour, P.; Ecker, D.; Global Biomanufacturing Trends, Capacity, and Technology Drivers: Industry Biomanufacturing Capacity Overview. American Pharmaceutical Review, June 30, 2017.
[41] http://www.borealisbiotech.com/images/Determining_the_Cost_of_Manufacturing_a_Biologic_Product.pdf
[42] https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/rapid-growth-in-biopharma
[43] https://www.japantimes.co.jp/news/2017/05/16/business/corporate-business/samsung-looks-beyond-smartphones-next-generation-biologics-market/#.W1foM9VKjGg
[44] http://www.bioprocessintl.com/manufacturing/facility-design-engineering/construction-and-start-up-costs-for-biomanufacturing-plants-182238/

Rentschler Biotechnologie conducted a study comparing manufacturing costs under two scenarios which include the use of a stainless steel bioreactor and single use bioreactors. The analysis examined the net present cost of building 15,000 liter and 2,000 liter stainless steel reactors and 2,000 liter single use reactors. Only at the highest levels of production did the 15,000 liter stainless steel reactors have a lower net present cost. This highlights the additional value of flexibility afforded by the single use reactors when small and medium batch sizes are the mainstay of production. It also illustrates that except for the products with the highest and most consistent demand, single use bioreactors have a cost benefit advantage.

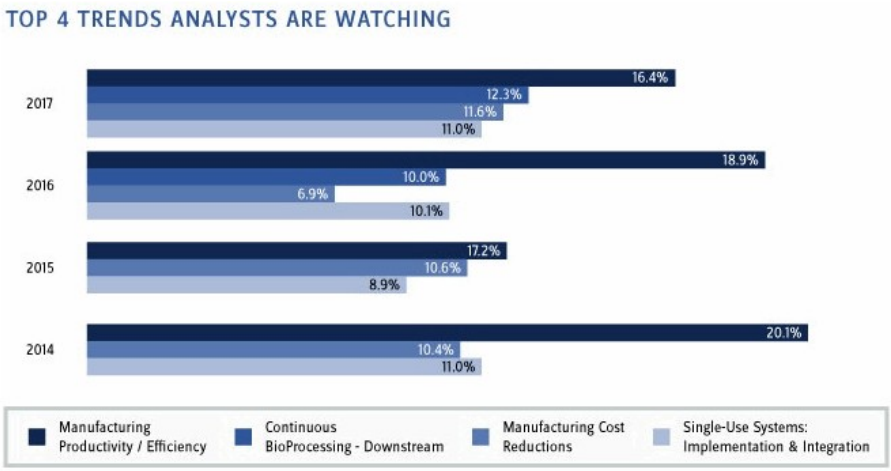
Exhibit XIII – Comparison of Facility Types on Net Present Cost (NPC)[45]



An article published in Biopharma Reporter evaluated a study conducted by Baxter BioSciene Lessines which identified several factors supporting single use equipment. The study compared two 2,500 liter stainless steel bioreactors with two 2,000 liter single use reactors. The output difference was only 10% lower in the stainless steel despite a 20% smaller capacity. While material cost was 35% higher for single use, the overall cost was less due to the lower requirement for personnel, utilities and, most importantly, capital expenditure. Construction time for new single use plants is shorter, allowing for capacity to come on line more quickly.[46]

An article featured in Bioprocess Online highlighted the top four industry trends over the 2014 to 2017 period. The most cited area for all four years was manufacturing productivity and efficiency. We think this means there is an opening for new approaches to recombinant protein expression and for expanded use of single use bioreactors.

Exhibit XIV – Top Four Trends in Biopharmaceutical Production[47]



[45] Rentschler Presentation by Dr. Frank Gießelmann, Director USP Production. Stainless steel or plastic? The Rentschler decision process BPI West, March 1, 2017
[46] https://www.biopharma-reporter.com/Article/2015/04/29/Single-use-will-never-fully-replace-stainless-say-biologics-makers
[47] Source: 14th Annual Report & Survey Biopharmaceutical Capacity and Production, April 2017, BioPlan Associates, Inc.

Partners, Collaborators and Manufacturers

Dyadic's R&D efforts are carried out through its contract research organization (CRO) relationships with Biotechnology Developments for Industry in Pharmaceuticals, SLU (BDI), VLPbioSLU (VLP) and VTT Technical Research of Finland (VTT). BDI and VLP will undertake gene expression work and current good manufacturing practice (cGMP) media development combined with fermentation optimization work. The goal of these efforts is to improve yields, turnaround time and purity of vaccine, antibody, enzyme and other therapeutic protein production. VTT will focus on continuing to modify the genetic properties of the C1 cells in order to glycoengineer them so the proteins produced from C1 more closley resemble human like glycosylation structures. The work is also expected to further improve yield, stability and purity of the proteins prodiuced from C1, such as the efforts related to the ongoing protease deletion work.

BDI and VLP are both subsidiaries of the company Spanish Biotechnology Developments for Industry, SL. The partners are providing research services and a service framework agreement that will develop C1 for a variety of projects:

- Proof of concept research collaboration for molecular biology enzymes used as reagents
- VLP development
- Human and animal therapeutic proteins (mAbs, Fabs, bi-specifics)
- Certolizumab (Cimzia) – recombinant humanized Fab antibody fragment
- Blinatumomab (Blincyto) – bi-specific T-cell engager for ALL

The R&D agreement with BDI will have a duration of two years and will emphasize development of vaccines and drugs employing the C1 platform. The BDI team has previous experience developing C1 gene expression and industrial fermentation and will use this experience to further advance the fungus toward commercialization in the biopharmaceutical space. All output generated under the agreement is property of Dyadic. Dyadic prefunded the R&D efforts and paid €1 million as an engagement fee and received a 16.1% equity interest in BDI and a 3.3% equity interest in VLP.

Certolizumab (Cimzia) is manufactured by UCB and used to treat Crohn's disease, arthritis and other autoimmune disorders. The drug is an antigen binding fragment (Fab) in the tumor necrosis factor (TNF) α inhibitor class that suppresses inflammation. The biologic is non-glycosylated, which makes it an appropriate first pursuit for C1 production. The primary goal of expressing certolizumab is to verify that C1 can generate a molecule identical to Cimzia with similar performance, quality and safety as the approved product. Dyadic and BDI eventually plan to pass certolizumab to a biosimilar developer after they have completed preclinical work. Certolizumab is expected to generate about $1.7 billion in revenues in 2018[48] and could see biosimilar competition by 2023. Assuming that a biosimilar could obtain 10% market share at a 30% discount to the branded biologic[49] and a 3% royalty to Dyadic, this could equate to $3.6 million in royalties.[50] In the exhibit below, we show Dyadic's portfolio of candidates.

Exhibit XV – In-House Development of Biosimilars

Candidate	Structure	Applications	Market Volume (*) ($M)	Status (30L Fermentation)
SP-VP2 (extracellular)	VLP 	Animal Vaccines	N/A	0.3 g/L (114 h) 0.063 g/L/d
Pembrolizumab (Keytruda)	mAb (IgG1)	Oncology	1,402	1.1 g/L (139 h) 0.18 g/l/d (**)
Bevacizumab (Avastin)			7,000	On Going
Infliximab (Remicade)			6,900	0.1 g/L (112 h) 0.021 g/L/d
Nivolumab (Opdivo)	mAb (IgG4) 	Inflammatory diseases	4,700	2.1 g/L (112 h) 0.45 g/L/d
Certolizumab pegol (Cimzia)	PEGYlated-Fab 		1,500	7.5 g/L (112 h) 1.6 g/L/d
Blinatumomab (Blincyto)	Bi-specifc scFV 	Oncology	~250	0.6 g/L (116 h) 0.12 g/L/d
Ranibizumab (Lucentis)	Fab 		4,250	On Going

[48] Evaluate Pharma estimates.
[49] Evaluate Pharma data. We examined a portfolio of biologics with biosimilar competition, especially Enbrel and Remicade to estimate potential market penetration.
[50] 2018 certolizumab revenues of $1.7 B x 10% share = $170 mm. $170 mm at 30% discount = $119 mm. 3% royalty on 119 million is $3.6 mm.

Dyadic is also working on a program to express antigens with the Zoonoses Anticipation and Preparedness Initiative (ZAPI) project. ZAPI is an EU-based public and private partnership stemming from the Innovative Medicines Initiative that is building a capability to respond to new infectious disease threats that could potentially be pandemics. The initiative seeks to develop a platform for the development and production of vaccines to address animal and human health. Murine animal studies were conducted and they concluded that the C1 antigen was able to produce an immune response and that there were no adverse events. Further preclinical testing is expected as is additional work for C1 strain and process optimization. The company believes the recent expression results are favorable as VTT reported that they were successful in obtaining ~723 mg/l expression of the ZAPI antigen. This result is several fold higher than the initial target expression level set by the ZAPI consortium and far higher than the expression levels of the alternative expression host being evaluated. Based on these encouraging results Dyadic anticipates that ZAPI will carry out additional animal studies with the C1 expressed antigen and expects that ZAPI will submit a regulatory filing with respect to the antigen produced by C1.

The Israel Institute for Biological Research is using C1 to develop recombinant vaccines and neutralizing agents of targeted antigens and monoclonal antibodies to address emerging diseases and threats. If successful, the products may transit to clinical trials, GMP manufacturing and the regulatory approval process in Israel.

Dyadic is working with some of the largest global biopharmaceutical companies. Not only do the partners contribute to the funding of R&D, they also have a first look into its capabilities and will likely be the first to bid on the C1 technology if Dyadic is acquired. The interest of several large pharmaceutical companies lends credence to C1's potential as an alternative expression platform. Deep pockets and experienced regulatory teams are critical to launching a first commercial product expressed by C1, and these partners have that capability. The latest collaboration announced was with Sanofi-Aventis in September 2018. A list of public and nonpublic commercial partners includes:

- Mitsubishi Tanabe Pharma
- Israel Institute for Biological Research
- Undisclosed biopharma producing monoclonal antibody "X"
- Undisclosed biopharma producing monoclonal antibody "Y"
- Undisclosed collaborator for bi-specific expression
- Undisclosed collaborator for FC-fusion proteins
- Sanofi-Aventis proof of concept to produce biologic vacccines and drugs of interest
- Zoonoses Anticipation and Preparedness Initiative (ZAPI)

Intellectual Property

Dyadic has been granted 20 patents worldwide on the C1 cell line. Patents filed prior to 2016 were sold to DuPont for industrial uses and Dyadic was granted back a co-exclusive license and exclusive right to sublicense C1 for animal and human pharmaceutical applications. Dyadic maintains the right to develop and sublicense the C1 technology in human and pharmaceutical applications. We note that even though there is patent protection for C1, it will be difficult for another company to replicate what has evolved from years of laboratory work. Therefore, we see the primary threat to C1 emerging from an alternate expression system rather than from copies of the C1 strains that will be used in production. Below we list Dyadic's most relevant patents.

Exhibit XVI – Patent Listing

Patent #	Patent Titles	Filed
8,871,493	Transformation system in the field of filamentous fungal hosts	17-Sep-12
8,680,252	Expression and high-throughput screening of complex expressed DNA libraries in filamentous fungi	10-Dec-07
8,268,585	Transformation system in the field of filamentous fungal hosts	13-Mar-08
8,673,618	Construction of highly efficient cellulase compositions for enzymatic hydrolysis of cellulose	20-Oct-10
8,551,751	BX11 enzymes having xylosidase activity	5-Sep-08
8,304,212	Methods and compositions for degradation of lignocellulosic material	10-Jul-07
7,923,236	Fungal Enzymes	2-Aug-07
7,906,309	Expression-regulating sequences and expression products in the field of filamentous fungi	17-Apr-01
7,892,812	Chrysosporium cellulase and methods of use	30-Sep-97
7,883,872	Construction of highly efficient cellulase compositions for enzymatic hydrolysis of cellulose	13-Jul-06
7,794,962	High-throughput screening of expressed DNA libraries in filamentous fungi	21-Jul-06
7,399,627	Transformation system in the field of filamentous fungal hosts	21-Mar-03
6,015,707	Treating cellulosic materials with cellulases from chrysosporium	29-Jun-98
5,811,381	Cellulase compositions and methods of use	10-Oct-96

Corporate Milestones

Dyadic is currently working with multiple partners to develop C1 and familiarize regulatory authorities with it. Biopharmaceutical partners are funding various research and development programs which has led and is expected to continue to lead to further improvements in C1's performance. The company anticipates such research will also lead to clinical trials for molecules produced from C1. We list some of the key milestones that we see on the horizon for Dyadic. Over the next year or two we anticipate the following events to take place.

- ZAPI progress update – 2H:18
- Glyco-engineering modifications - 2019
- Accelerate C1 expression time to less than 3 months – 1Q:18
- Develop low cost media without yeast extract – 1Q:18
- Achieve target yields (mAbs, Fc-Fusion, Fab) – 2Q:18
- Validate protease expression library – 2Q:18
- Deletion of eighth protease gene – 2Q:18
- Achieve target yield for igG monoclonal antibody (mAb) (2.46 g/l/d) – 3Q:18
- Achieve target yield for antibody fragment (Fab) certolizumab (2.0 g/l/d) – 3Q:18
- Sanofi-Aventis Deutschland GmbH collaboration – 3Q:18
- Initiate fully funded proof of concept synthetic pathway engineering of C1 for metabolite production - 2019
- Develop metabolic model for use in the existing and future metabolite programs - 3Q:18
- File Form 10 / Convert to SEC Reporting Company – 1Q:19
- Sanofi-Aventis research project completion – 2H:19
- Completion of 2-year R&D agreement with BDI and VLP – mid-2019
- Enter into partnership for further development of certolizumab - 2H:19
- Enter into additional research collaborations – 2019

2Q:18 Financial Results

Dyadic International filed a press release announcing second quarter 2018 results on August 9, 2018 in conjunction with their quarterly report. The company highlighted its fourth research collaboration (and shortly after announcing a fifth with Sanofi-Aventis) achieved this year as well as reaching record production levels for C1 of 2.4 g/l/d to produce mAbs and 1.9 g/l/d for Fabs. Progress eliminating protease genes and improvements in process and media optimization has contributed to higher output and lower cost. The company also received shareholder approval to conduct a reverse stock split if needed to obtain a NASDAQ listing and has extended its existing share repurchase program for another year.

Revenue of $161,000 represented research collaborations in 2Q:18. Total operating expenses were $2.0 million, up 17% compared to 2Q:17. Higher R&D was offset by lower G&A expense. Net loss was ($1.6) million and ($0.06) per share. This compares to a net loss of ($1.3) million in 2Q:17. Average share count declined from 28.7 million in 2Q:17 to 28.1 million in 2Q:18 reflecting the impact of the company's share repurchase program.

Research and development expenses of $942,000 increased from $420,000 in the prior year period due to additional internal research activities with third party CROs, personnel related costs and the addition of development costs related to BDI. General and administrative expenses fell to $922,000, a 25% decline over prior year levels attributable to reductions in legal and litigation costs, elimination of compensation costs related to the former CFO, lower share-based compensation expenses and other cost reductions. Exchange rate volatility between the US dollar and Euro resulted in a small foreign currency gain in the period. Interest income from average cash, investments and equivalents balance of ~$46 million was $220,000

Cash burn was ($1.7) million in the quarter and ($2.4) million for the first six months of 2018 as a number of non-cash and favorable changes in balance sheet items were recognized. Zero cash was used in financing in the second quarter, and ($375,000) was used in the first six months which represented repurchases of common stock. As of June 30, 2018, cash, equivalents and investment securities totaled $45.4 million or $1.61 per share. Dyadic carries no debt on its balance sheet.

Dyadic has had a stock repurchase program in place that has retired over 13 million shares from January 2016 to June 30, 2018, at an average price of $1.53 representing $19.9 million in total purchases. On August 6th, the board of directors extended the existing stock repurchase program for another year which authorized the repurchase of up to $5 million of shares. $4.1 million of authorization remains under the program.

RISKS

All investments contain an element of risk which reflects the uncertainty of the business and what it will ultimately achieve. Some investments exhibit higher predictability, with current cash flows and established sales. These enterprises will have a lower level of perceived risk while other companies that are developing an undefined, new technology that have not yet received regulatory approval have a much higher level of perceived risk.

The biotechnology space includes companies at both ends of the spectrum, from mega-cap pharmaceutical powerhouses that have multiple products currently generating revenues, to small operations with a handful of employees conducting pre-clinical studies. Many of the risks faced by the large pharmaceutical companies and smaller biotechnology-focused firms are similar; however, there are some hazards that are particular to smaller companies that have not yet established themselves or their products.

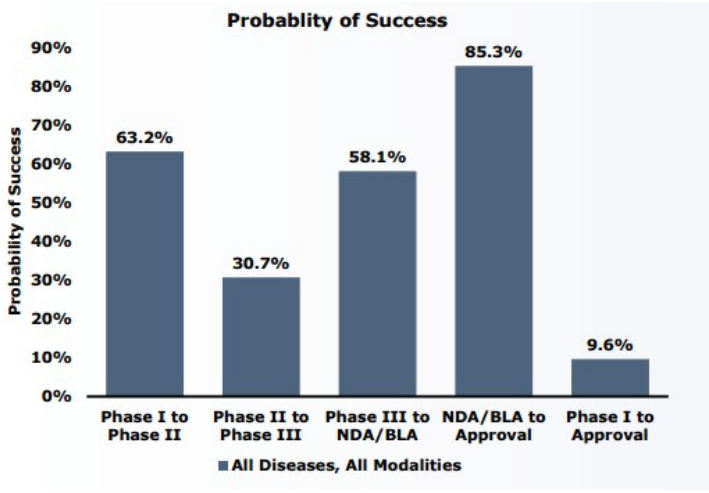
For smaller early-stage companies, investing in drug development is an extended process. The timeframe for conducting pre-clinical research to eventually commercializing a drug can take from 12 to 15 years or even longer given market conditions. And with, on average, only one in one thousand compounds eventually making it to the market, the risks are substantial.

Even if a company has a strong, experienced team that is developing a therapy with a high likelihood of success and a large addressable market, securing funding may pose a substantial risk. Access to financing comes and goes in cycles. During periods of improving confidence, capital may be easy to access; however, during a liquidity crisis or a period of heightened risk perception, even companies with bright prospects may be in trouble if they are dependent on the financial markets to fund their work. If capital is needed to sustain operations and it is not readily available, the company may be forced to suspend research and development, sell equity at a substantial discount to previous valuations and dilute earlier shareholders. A lack of funding may leave potentially promising technologies without a viable route to follow or force a company to accept onerous terms. Dyadic holds an enviable position in the world of development stage companies as it holds enough cash on its balance sheet to fully fund its planned development program. Furthermore, much of the company's research and development activities are financially supported through partner efforts to develop recombinant proteins using the C1 expression platform.

All drugs and manufacturing processes must navigate the regulatory approval process in the US, EU and other countries before commercialization in those regions. The outcome of this effort is a material uncertainty which may take years depending upon the needs and desires of the determining authority. Substantial expense is undertaken to bring a molecule or compound through clinical trials and address all of the regulatory agencies' concerns. History has shown that regulatory agencies favor known processes, biological targets and mechanisms of action when granting approval for a therapeutic agent. New methods, targets and mechanisms of action face additional scrutiny by regulatory agencies, which may increase the development time, cost and probability of success of these medicines and technologies. Isolating companies that have a long history of research success in drug development, with opinion leaders and experts in the field are important fundamentals that can help mitigate these risks. Companies that have had previous success with the FDA or other regulatory agencies also are more attractive than those who may be new to the process. Dyadic is working with many established pharmaceutical companies that have the resources and experience to overcome these challenges.

In the following exhibit we highlight success rates for new chemical entities submitted to the FDA. We believe the application of a similar probability framework is applicable to Dyadic as the success of its C1 expression system relies on approval of the biologics it produces. We apply a 15% probability of ultimate commercialization of products using the C1 platform based on the data generated in the Clinical Development Success rates analysis cited below. Our estimates will reflect improved probability of success as development moves along the continuum of clinical trials and we achieve discrete regulatory milestones and regulatory approval.

Exhibit XVII – Success of Phased Trials and Regulatory Approval[51]



In recent years, CROs have taken on a larger role in the development of drug candidates as the complexity and cost of trials has increased. Dyadic is particularly reliant on CROs as it does not maintain an internal R&D function. Finding appropriate populations to participate in clinical trials has become increasingly difficult due to the shift to personalized medicine and orphan indications that address a small population. This shift has increased the dependence on these specialized CROs for project management and clinical monitoring services which add additional risks and dependence on third parties.

In addition to CROs, Dyadic relies on partners for manufacturing and analytical testing. Risks of poor manufacturing processes, quality control issues and product delays may postpone ultimate production of a drug if partners are out of compliance with regulatory agency requirements. Dyadic has developed relationships with its partners, has hired specialists to monitor and direct progress and has implemented a process to ensure good practices and compliance. While the company has made efforts to ensure a productive relationship, the partner may lack the desire or skill to successfully maintain the required good practices and the partner may have other competing products under its control that receive greater attention and focus.

Drug price inflation has gained increased attention over the last several years and has contributed materially to the increase in health care costs over the last decades. As new therapies have been approved, drug prices have set new records and increased at a substantial rate. Biologics are one area that has been particularly noteworthy with respect to cost. Recent examples such as BioMarin Pharmaceuticals' Brineura costs over $700,000 for a full year of treatment, Biogen's Spinraza for spinal muscular atrophy is $750,000 for the first year of treatment, and last year's approved CAR-T therapies run from $400,000 to $500,000 per year of treatment.

Several risks arise from ever expanding price increases. Health care may become unaffordable for a broad segment of the population, reducing the market size to a level below what we could otherwise reasonably forecast. Pharmacy benefit managers and other third party payers may continue to remove drugs from their formularies due to price concerns and sharp price increases will attract the attention of elected officials and regulators who may create legislation and implement regulations that limit drug profitability. Additionally, the government may impose additional non-price related regulation and disclosure requirements that can increase costs for the industry. This risk may represent a tailwind for Dyadic as its expression system may provide a material reduction in costs for manufacturing biologics, thereby incentivizing its use.

While we have discussed a broad variety of risks above, we believe that our forecast parameters, discount rates, success probabilities and valuation metrics address these eventualities and our target price reflects an assumption of these risks faced by all biotechnology companies.

[51]Clinical Development Success Rates 2006-2015. David Thomas, Justin Burns, John Audette, Adam Carroll, Corey Dow-Hygelund, Michael Hay.

PEERS AND COMPETITORS

There are many participants in in the recombinant protein expression market, with some of the largest global companies such as Samsung, Lonza and General Electric Healthcare involved in many aspects of the industry. Universities are deeply involved in research and development activities and many times partner with public and private companies to advance the science. There are distinct areas in protein expression, from the manufacturing end which includes both immense stainless steel bioreactors to smaller operations that use single-use disposable bioreactors. The industry also includes manufacturers of equipment, media, expression cells and consultants that will guide R&D activities for cell line development and contribute specialty mammalian, bacterial, fungal or other systems for protein expression. Below we provide a summary of many of the prominent contributors in this area. Dyadic is somewhat unique in that it is a developer of a new expression system that may potentially compete with the status quo.

Exhibit XVIII – Peers and Potential Competitors[52]

Ticker	Company	Price	MktCap (MM)	EV (MM)	Description
4974.T	Takara Bio	¥3,150	¥379,310	N/A	Next generation sequencing, stem cell research, protein research, PCR, cloning and gene function.
ABC.L	Abcam PLC	£14.32	£2,930	£2,880	Producer and marketer of high quality protein research tools. These tools enable life scientists to analyse components of living cells at the molecular level which is essential in a wide range of fields including drug discovery, diagnostics, and basic research.
BDX	BD Biosciences	$261.00	$69,830	$90,860	Flow cytometry products provider. Instruments including cell analyzers & sample prep, reagents for research & clinical purposes, cell culture media, media supplements and bioprocessing services.
BIO	Bio-Rad Laboratories	$312.99	$9,280	$8,820	Provides PCR, chromatography, transfection, electrophoresis and other services. Also provides clinical diagnostics, spectroscopy, process separations and other products and services.
CDXS	Codexis	$17.15	$918	$966	Protein engineering with its CodeEvolver protein optimization process. proteins are stable and predictable, environmentally friendly and offer performance characteristics that can dramatically improve quality and efficiency. In addition to delivering more sustainable processes and producing minimal waste, engineered proteins can also produce higher yields to reduce costs and improve ROI.
GNNSF	GenScript Biotech	$1.72	$3,130	$3,170	Biologic Services including antibody lead generation, lead optimization, production and testing. GenScript also performs target discovery. Other services include cloning kits, DNA, gene and peptide synthesis.
HZD.L	Horizon Discovery Group PLC	£2.10	£315	£293	Cell lines, screening, cell based assays, animal models. Optimization of drug development through use of genetic data, knowledge of biological pathways, and specific patient identification.
LZAGY	Lonza Group	$34.04	$25,600	$28,950	CDMO supplier to the pharma and biotech industry. Discovery, development, manufacture and distribution. Bioreactor biologics manufacturing with mammalian cell culture (mAb, recombinant proteins, microbial fermentation, cell therapy & gene therapy).
MRK.DE	Merck Millipore Sigma	€ 89.00	€ 38,700	€ 48,950	Research, process and applied solutions for biopharma customers developing and manufacturing.
NVZMY	Novozymes A/S	$54.74	$18,730	$16,450	Enzyme development mostly for household care, food and agricultural use. In December 2017, Novozymes divested Albumedix, its stand-alone pharma entity which was separated from Novozymes in 2016.
QGEN.VI	Qiagen	€ 31.48	€ 7,310	N/A	Services including sequencing, molecular diagnostics, life science research, bioinformatics, PCR.
RGEN	Repligen Corp	$55.46	$2,430	$2,280	Upstream & downstream bioprocessing, filtration, cell culturing, purification, protein A resins & ligands. ELISA kit analytics.
SNY	Sanofi	$44.67	$110,250	$134,200	Large biopharma with a broad offering of drugs, biologics, products and services.
TMO	Thermo Fisher Scientific	$244.08	$98,310	$116,470	Broad portfolio of products and services for life science. PCR assays, antibodies, cell culture & transfection agents, manufacturing & processing,

[52] Source: Yahoo Finance. Price and market capitalization data is as of September 28, 2018

Ticker	Company	Description
pvt	Accelagen Inc	Antibody production, GPCRs, kinases, nuclear receptors, and many other classes of drug targets and therapeutic proteins. Uses Baculovirus Expression Vector System (BEVS), E. coli expression, mammalian expression, Wave Bioreactors, Cell Factory, and AKTA chromatography systems for protein purification.
pvt	Addgene Inc.	Plasmid repository
pvt	ARTES Biotech	Cell line development based on yeast & bacteria, process development, manufacturing,
pvt	BIA Separations	Biochromatography provider. Monolithic high performance liquid chromatography columns, for downstream processing of proteins and other molecules. Provides process development and immobilization of antibodies services.
pvt	Boehringer Ingelheim	Broad portfolio of services which include biotech plans for mammalian cell culture fermentation. Contract manufacturerof biologics for 15/20 top global pharmas. BI BioXcellence is the CMO for BI.
pvt	Domainex Ltd.	Integrated medicines researches offered to global academic, pharma & biotech organizations. Drug discovery services, protein expression, assay development & medicinal chemistry for lead optimization.
pvt	Geneva Biotech	Private, research focused and developing a portfolio of viral & nonviral DNA delivery systems that provide better ways to deliver DNA into cells. Uses Insect cell, Mammalian & primary cell and E. Coli expression systems.
pvt	Irvine Scientific	Global life sciences and medical media provider. Industrial cell culture, express media services, spent media analysis. Provide stem cell and primary cell culture media, recombinant growth factors, serum & other products.
pvt	Jena Bioscience	Provide nucleotides and nucleosides, genomics analysis services,
pvt	JR Scientific	Contract manufacturer of high volume standard and custom serum & sterile liquid filtered products used by pharma, biotech, vaccine, university, and research institutions. Provides disposable processing, custom manufacturing, cell culture testing & cleanroom services.
pvt	LifeSensors	Ubiquitin drug discovery; providing both services and products focused on the ubiquitin vertical.
pvt	Lucigen Corp	Gene editing, sequencing, and wide variety of other genomics products. Core competencies include enzyme evolution, protein expression, cloning, competent cells, next gen sequencing, and molecular diagnostics.
pvt	New England Biolabs	Cloning & synthetic biology, DNA amplification, genome editing, cellular analysis, protein expression & purification. Also tools to modify DNA, enhance cloning and undertake data analysis.
pvt	Pall Industries	Provides filtration, separation and purification services to a variety of industries including biotech, food, industrial manufacturing, power generation, microelectronics, aerospace, oil & gas and others.
pvt	Peak Proteins	Provides protein expression, purification (chromatography), crystallography and structural determination using x-ray crystalography. Can express protein in E. coli, baculovirus/insect cells and mammalian cells.
pvt	Profacgen	NY-based protein service provider offering protein expression & purification, protein interaction analysis, high-throughput screening and protein engineering.
pvt	Promega Corp	Cell biology, DNA analysis, drug development, genetic identity, lab instruments, molecular diagnostics, protein analysis and RNA analysis. Focused on environment, plant, food, water testing and clinical research.
pvt	ProteoGenix	Drug discovery services including peptide synthesis, protein production, antibody production & gene synthesis. Recombinant Protein Expression in five systems (*E. coli*, *B. subtilis*, yeast, *P. pastoris* and *S. cerevisiae*, insect cells and mammalian cells).
pvt	RainDance Technologies	Digital PCR, next generation sequencing target enrichment,
pvt	Selexis	Cell line development, lead identification, genomic characterization. Maintains proprietary CHO-K1 cell line.
pvt	Sengenics	Functional proteomics company using proprietary technology for autoantibody biomarker discovery, drug companion diagnostics, infectious diseases & vaccines & protein interaction assays.
pvt	Synthetic Genomics	Tools for reading and writing the genetic code. RNA replicons & BioXp DNA printer system. Optimize organisms for bioproduction/cell factories. Has Vmax, a prokaryotic host to generate biomass.
pvt	Viva Biotech	Drug discovery products & services. Areas of focus include protein science, structure based drug design (SBDD), fragment based drug design (FBDD), affinity selection mass spectrometry (ASMS) screening technology, and membrane protein targeted drug discovery. Includes cell lines, crystal structures, GPCR proteins and antibodies.

MANAGEMENT AND BOARD PROFILES

Dyadic has a superb management team with its CEO, Mark Emalfarb having led the company, other than from April 2017 to June 2018, since 1979. His first enzymatic venture developed a system that would more efficiently produce stonewashed jeans. As the company progressed, it expanded into the industrial manufacturing arena where the C1 system was used in the bioenergy, biofuel, chemical, industrial enzyme and other industrial application areas. Now the focus has turned to biopharmaceuticals and a new team has been added with experience in biomanufacturing, process optimization, and life sciences business development. The board of directors has a background in R&D research, bioprocess development, and has held senior positions in large pharma including Merck and Pfizer. The experience of the board allows them to assume a dual role of both board of directors and scientific advisory board.

Mark A. Emalfarb, Founder, Chief Executive Officer (CEO), and Director

Mark Emalfarb is the founder of Dyadic, and currently serves as the CEO and Director on the Board of the company. He has been a member of the board of directors and has served as its Chairman from October 2004 until April 2007 and from June 2008 until January 2015. Since founding the predecessor to Dyadic in 1979, Mr. Emalfarb has served as a Director, President and CEO and has successfully led and managed the evolution of Dyadic from its origins as a pioneer and leader in providing inputs used in the stone-washing of blue jeans to the discovery, development, manufacturing and commercialization of specialty enzymes used in various industrial applications and the development of an integrated technology platform based on Dyadic's patented and proprietary C1 fungal microorganism. Mr. Emalfarb is an inventor of over 25 US and foreign biotechnology patents and patent applications resulting from discoveries related to the C1 fungus, and has been the architect behind its formation of several strategic research and development, manufacturing and marketing relationships with U.S. and international partners. Mr. Emalfarb earned his B.A. degree from the University of Iowa in 1977.

Ronen Tchelet, Ph.D., Vice President of Research and Business Development

Ronen Tchelet, Ph.D. joined Dyadic in May 2014, and has been VP of Research and Business Development since January 2016. Dr. Tchelet has been a key contributor to Dyadic's transformation into a pharmaceutical biotech company. Prior to joining Dyadic, he was the founder and Managing Director of Codexis Laboratories Hungary (CLH) and a VP of Codexis Inc. from 2007 through 2014. While at CLH, Dr. Tchelet established a state-of-the-art laboratory for strain engineering and all aspects of fermentation including process optimization and scale up. During this period, he also led a collaboration that successfully developed C1 technology for Biofuel and Bio-Industrial enzymes applications. Dr. Tchelet's experience in the pharmaceutical industry includes prior employment at TEVA Pharmaceutical, API Division. While at TEVA, he served as a Chief Technology Officer of Biotechnology and head of TEVA's Biotechnology Research and Development fermentation plant in Hungary. Dr. Tchelet was also the Director of Quality Assurance for COPAXONE. Throughout his career, Dr. Tchelet has led several Biotechnology and Biosimilar projects that have encompassed all aspects of research and development, operations management, and manufacturing of API's and biologics. Dr. Tchelet received his Ph.D. in Molecular Microbiology and Biotechnology from Tel Aviv University in 1993 and did his postdoctoral work as an EERO fellow at the Institute of Environmental Science and Technology in Switzerland.

Ping W. Rawson, Chief Accounting Officer (CAO)

Ping Rawson was promoted CAO in March 2018. She currently serves as the principal financial officer and is responsible for all aspects of finance, tax and treasury. Prior to joining in June 2016 as Director of Financial Reporting, Ms. Rawson served as a technical accounting management position for ADT security services, where she led accounting and financial reporting workstream for acquisition, integration and restructuring. Prior to that, Ms. Rawson was an accounting research principal for NextEra Energy where she was responsible for accounting research and new standards implementation. Previously, Ms. Rawson was a manager at Deloitte in New York City, where she was a subject matter specialist for derivatives, financial instruments and valuation, providing audit, SEC reporting, and capital markets consulting services to large banking and multinational public companies in the financial service industry. Ms. Rawson holds both a MBA in Finance, and an MS in Accounting from the State University of New York at Buffalo, and a BS in Economics from Guangdong University of Foreign Studies in China. She is a certified public accountant in the state of New York.

Matthew S. Jones, Chief Commercial Officer

Matthew Jones joined Dyadic in May 2016 and serves as Chief Commercial Officer to lead Dyadic's strategic partnerships, licensing and commercial opportunities within and across the biopharmaceutical industry. A veteran of the life sciences industry with two decades of commercial deal making and leadership experience, he has developed and implemented strategies which have delivered revenue growth, organically and through acquisitions, for a diverse range of life science businesses both in Europe and the US. Mr. Jones previously served as Chief Commercial Officer for Concept Life Sciences from its formation until 2016. Prior to that, he was VP of Global Sales & Business Development at Lonza Biologics, implementing new income generating revenue streams and capturing enterprise synergies in manufacturing, research and client/vendor relationships. From 2009 to 2012, Mr. Jones served as EVP of Business Development & Marketing at Ricerca Biosciences, responsible for strategic partnerships, royalty and asset license optimization and marketing effectiveness and where he supported the Bain Ventures trade sale of the business toward WiL research. From 2003 to 2009, Mr. Jones was SVP of Business Development at MDS Pharma Services, where he was responsible for global biopharmaceutical and clinical commercial growth strategies. Earlier in his career, Mr. Jones also held senior level leadership roles within the biopharmaceutical industry with Alkermes and GlaxoSmithKline. Mr. Jones is a graduate of Warwick University and London Business School.

Michael P. Tarnok, Chairman, Director

Michael P. Tarnok joined Dyadic's board of directors on June 12, 2014 and has served on the Company's audit, nominating and compensation committees, and on January 12, 2015 Mr. Tarnok was appointed Dyadic's Chairman of the Board of Directors. Mr. Tarnok is also currently a board member of Global Health Council, and Ionetix, Inc. In addition, Mr. Tarnok's prior board service includes Keryx Biopharmaceuticals, Inc., where he also served as Chairman of the Board. Mr. Tarnok is a seasoned finance and operational executive with extensive pharmaceutical industry experience in a wide range of functional areas. He spent the majority of his career at Pfizer Inc., which he joined in 1989 as Finance Director-US Manufacturing and from 2000 to 2007 served as a SVP in Pfizer's US Pharmaceutical Division. In this position, Mr. Tarnok managed multiple responsibilities for the division including, finance, access contracting, trade management, information technology, Sarbanes-Oxley compliance and the Greenstone generics division. Prior to joining Pfizer, Mr. Tarnok worked primarily in financial disciplines for ITT Rayonier, Inc., Celanese Corporation and Olivetti Corporation of America. Mr. Tarnok earned an M.B.A. in Marketing from New York University and a B.S. in Accounting from St. John's University.

Arindam Bose, Director

Arindam Bose, Ph.D. joined Dyadic's board of directors on August 15, 2016 and serves on the Company's audit and nominating committees. Dr. Bose retired from Pfizer Worldwide Research & Development in 2016 after 34 years in leadership roles in bioprocess development and clinical manufacturing. Most recently, Dr. Bose served as Vice President, Biotherapeutics Pharmaceutical Sciences External Affairs and Biosimilar Strategy with responsibility for external sourcing, competitive intelligence and external influencing as well as for executing the technical development plan for Pfizer's entry into biosimilars. He is widely recognized as a Key Thought Leader in the biopharmaceutical industry. Dr. Bose has served as the Chair of the Biologics and Biotechnology Leadership Committee of the Pharmaceutical Research and Manufacturers of America (PhRMA), the chief advocacy arm of the US pharmaceutical industry. His outstanding accomplishments and service to the profession have been recognized by his election as "Fellow" of three leading professional organizations: American Chemical Society, American Institute of Chemical Engineers and American Institute for Medical and Biological Engineering. Dr. Bose was elected to the US National Academy of Engineering in February 2017 for innovative research in biologics manufacturing. He received a Ph.D. in chemical engineering from Purdue University, a M.S. from the University of Michigan, Ann Arbor and a B. Tech from the Indian Institute of Technology, Kanpur.

Barry Buckland, Director

Barry C. Buckland, Ph.D. joined Dyadic's board of directors in January 2018. Dr. Buckland retired from Merck Research Laboratories in 2009 after 28 years of contributions to the Bioprocess R&D group including more than 12 years as leader in the position of VP. Since leaving Merck Research Laboratories, Dr. Buckland has headed up his own consulting company, BiologicB, LLC. He also is President of Engineering Conferences International (ECI), a not for profit organization which organizes prestigious conferences with an engineering focus. Dr. Buckland has chaired successful conferences such as Microbial Engineering I and Vaccine Technology Conferences I to IV. He is also a visiting professor at University College London in the Biochemical Engineering Department and is the author or co-author of more than 70 publications. His previous Board experience includes Enumeral Biomedical and Mucosis. Dr. Buckland was a Senior Advisor to Protein Sciences until they were purchased by Sanofi in 2017. Dr. Buckland became Executive Director of NIIMBL (National Institute for Innovation for Manufacturing Biopharmaceuticals) in 2017.

VALUATION

Dyadic is in an enviable position for a development company. It holds sufficient cash on its balance sheet to internally fund all development activities and return capital to shareholders. Additionally, the company receives revenues from development partners to fund certain research efforts that create additional intellectual property and C1 advancement that accrues to Dyadic. Partner revenues also offset some of the company's fixed costs, resulting in low cash burn as compared to most biotech companies. Our valuation approach employs two methods to generate revenue estimates for Dyadic.

The first approach estimates the total value of global biologics sales, citing estimates from a variety of sources[53,54,55] settling on a market size of $226 billion in 2018 and growing at an average 10% CAGR over the succeeding 5 years. After that we forecast a mid-single digit growth rate for the industry. To determine an appropriate royalty amount, we calculate how much value C1 can add as compared to current systems in use. We estimate that the average cost of goods sold in the upstream is about 6% of revenues. We apply this rate to the total industry to generate the pool of value C1 can address. To this pool, we assume a penetration rate of 2% in 2023 when we anticipate the first products to be approved and commercialized using C1. Over the next five years, our forecast calls for an increase in penetration to 10% by 2028, where it will hold steady. Then we calculate the amount of value C1 can generate. Our research found that C1 was six times as productive as CHO cells, reducing costs by 83%. We estimate that Dyadic can capture 25% of the cost reduction from biologics manufacturers which is equivalent to a royalty on revenues of 1 – 2%, depending on gross margin.

The second approach estimates Dyadic royalty revenues using total volumes of recombinant proteins produced. Based on cited resources we see about 27,000 kg of product being produced in 2018, growing to just over 47,000 kg in 2022.[56] Similar to our global market revenue approach, we see an initial penetration of 2% in 2022, growing to 10% in 2028 where it remains for the duration of our forecast. Based on our analysis discussed in the report we see an average cost reduction of $300 per gram by using C1 over other expression systems. We multiply the per gram savings by our market penetration assumption to generate total cost savings. We anticipate that Dyadic will be able to negotiate an amount equivalent to 25% of savings. This is equivalent to a royalty on revenues of approximately 1 – 2%, depending on gross margin. .

Over $1 billion of savings is achieved by 2024 by using C1 vs. CHO, assuming a 6% penetration rate. This grows to $3 billion by 2035 under our conservative estimates. As for royalty revenues accruing to Dyadic, the average of our approaches generates $78 million in 2022, $390 million by 2025 and $656 million by 2032. As part of our risk adjustment for drug development success, we apply a 15% probability of ultimate regulatory approval and commercialization, referencing the Clinical Development Success Rates cited in the Risks section of our initiation. This modification reduces revenue by 85% to produce probability adjusted royalty revenues. We also assume a small contribution of R&D revenue that is $1.4 million in 2019 and growing to $3 million by 2022 and increasing by 3% thereafter. These revenues come from partners who will develop C1 for their protein expression program. Partner R&D revenues will continue to carry a 20% gross margin.

R&D expenses are forecast to be $4.4 million in 2019, $5.0 million in 2020, $5.5 million in 2021 and reset at $2.0 million in 2023 as C1 begins to generate commercial product. G&A is estimated at $4.2 million in 2019, $4.6 million in 2020 and $4.8 million in 2021. In subsequent years it should grow at a 3% annual rate. Dyadic maintains NOLs to apply against future income and will continue to accrue additional NOLs until profitability is reached. Our forecast calls for first cash taxes of 28.9%[57] to be paid in 2026.

We use a 15% rate in our discounted cash flow (DCF) model and forecast cash flows until 2037. Our terminal growth rate is 2%. Current shares outstanding plus options exercised yields 31.5 million shares. With sum of parts valuation, cash from exercised options and cash on the balance sheet, we generate a $4.50 target price for Dyadic shares.

[53] Biologics Global Market Report 2018.
[54] Transparency Markets Research. Global Biologics Market: High Profitability and Increased Profit Margins through Premium Prices Encourage Growth, finds TMR. February 2018.
[55] Highsmith, Jackson. BCC Research. Therapeutic Drugs: Technologies & Global Markets. January 2015.
[56] Seymour, P.; Ecker, D.; Global Biomanufacturing Trends, Capacity, and Technology Drivers: Industry Biomanufacturing Capacity Overview. American Pharmaceutical Review, June 30, 2017. https://www.americanpharmaceuticalreview.com/Featured-Articles/188840-Global-Biomanufacturing-Trends-Capacity-and-Technology-Drivers-Industry-Biomanufacturing-Capacity-Overview/
[57] This includes the 21% federal rate, a 5% state rate and an additional 5% to address anticipated tax increase from state and federal sources to reflect increased deficits and fewer federal services assumed by the states.

CONCLUSION

Dyadic is in an enviable position having not only sufficient cash on its balance sheet to fund its development program but also receiving contributions from partners to advance C1 through the development process. Numerous collaborations with large, well-known pharmaceutical companies and government organizations lends a substantial level of credibility to C1's advance towards being a competitive expression system. Our conservative estimates call for a maximum of 10% penetration into the protein expression market and apply a 15% probability of ultimate commercialization. Additionally, we do not account for any cost savings for downstream activities, which could reduce costs by an additional amount[58] adding additional value to the platform.

The company has made substantial progress on a number of fronts. It has increased the productive capacity of C1 for a number of recombinant proteins, defined a low cost and effective media, reduced protease expression, began to modify glycosylation patterns and produced monoclonal antibodies with certain virtually indistinguishable properties such as ligand binding from CHO produced products among other achievements. We anticipate that C1 can produce a commercialized product by 2023.

While the protein expression industry is slow to change due to risk concerns from drug sponsors and regulatory agencies preferring familiar approaches, cost pressures may demand it. Biologics are some of the most expensive medicines on the market, partially due to their high and complex production costs. We anticipate a revolutionary change will come, forcing all parts of the health care ecosystem to reexamine cost structure. In the area of recombinant protein production, C1 provides an important solution that will be in demand, especially for more complex and higher cost proteins.

Dyadic represents a relatively low risk opportunity to assume a position in a revolutionary platform technology. With sufficient cash and funding to advance their program, there is almost no risk of dilution. With the company trading at near cash levels, we see investors acquiring the stock here gaining a billion dollar[59] technology for free.

Key reasons to own:

- **High cost of biologics production demands lower cost alternative**
- **C1 technology provides faster cell line development and production cycle**
  - **Technology addresses high cost component of drug manufacture**
  - **Favorable characteristics of productivity and purity**
  - **Less stringent operating conditions required**
  - **Low-cost synthetic growth media used**
  - **Avoids mammalian cell related viruses, reducing purification steps**
  - **Particularly beneficial for expensive, difficult to produce recombinant proteins**
- **Natural alignment between C1 and biosimilars/biobetters due to cost focus**
- **Development fully funded with cash on the balance sheet and partner contributions**
- **CEO holds dominant share of business and has history of cost conscious development**

In summary, we believe that Dyadic's C1 technology has provided substantial evidence of viability and flexibility, substantiated by collaborations with large, well known partners. Trading at cash levels, shares are substantially undervalued and should provide increasing upside as the company adds additional collaborators, achieves milestones and begins the clinical trial process for its first biologic. We initiate Dyadic International, Inc. at $4.50 per share.

[58] Dyadic has commissioned a study to evaluate the benefits and potential cost savings in the downstream segment of production. As more information becomes available regarding steps eliminated and specific costs reduced we will update our valuation estimate.
[59] Our estimates call for $1.1 billion is cost savings from the use of C1 by 2024 assuming a 6% penetration rate.

PROJECTED FINANCIALS

Dyadic International, Inc. - Income Statement

Dyadic International, Inc.	2016 A	2017 A	Q1 A	Q2 A	Q3 E	Q4 E	2018 E	2019 E	2020 E
Total Revenues	**$0.6**	**$0.8**	**$0.2**	**$0.2**	**$0.2**	**$0.2**	**$0.7**	**$1.4**	**$2.2**
YOY Growth		*28%*	*52%*	*-22%*	*-27%*	*27%*	*-2%*	*88%*	*57%*
Cost of R&D Revenue	$0.5	$0.7	$0.1	$0.1	$0.2	$0.2	$0.6	$1.1	$1.8
Provision for Contract Losses	$0.4	$0.2	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
R&D	$0.9	$1.8	$0.6	$0.6	$0.6	$0.6	$2.4	$2.8	$3.2
R&D Related Party	$0.0	$0.4	$0.4	$0.3	$0.4	$0.4	$1.5	$1.6	$1.8
G&A	$4.6	$5.0	$1.3	$0.9	$1.0	$1.0	$4.2	$4.2	$4.6
Foreign Currency Exchange	$0.1	($0.2)	$0.0	($0.0)	$0.0	$0.0	($0.0)	$0.0	$0.0
Income from operations	($6.0)	($7.1)	($2.2)	($1.8)	($2.0)	($2.0)	($8.0)	($8.3)	($9.1)
Operating Margin	*-1004%*	*-940%*	*-1210%*	*-1126%*					
Interest Income	$0.5	$0.6	$0.2	$0.2	$0.2	$0.2	$0.8	$0.7	$0.6
Other	$2.1	$4.4	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Pre-Tax Income	($3.4)	($2.2)	($2.0)	($1.6)	($1.8)	($1.8)	($7.2)	($7.6)	($8.5)
Provision for Income Tax	$0.2	($0.1)	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Tax Rate	*-7.1%*	*3%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
Net Income	**($3.6)**	**($2.1)**	**($2.0)**	**($1.6)**	**($1.8)**	**($1.8)**	**($7.2)**	**($7.6)**	**($8.5)**
Net Margin	*-609%*	*-282%*	*-1108%*	*-991%*					
Reported EPS	**($0.10)**	**($0.07)**	**($0.07)**	**($0.06)**	**($0.06)**	**($0.06)**	**($0.26)**	**($0.27)**	**($0.30)**
YOY Growth		*-25.2%*	*-202.8%*	*21.2%*	*19.1%*	*32.4%*	*246%*	*6%*	
Shares Outstanding	36.54	28.92	28.16	28.06	28.00	28.00	28.06	28.00	28.00

Source: Company Filing // Zacks Investment Research, Inc. Estim

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HISTORICAL STOCK PRICE

Dyadic International, Inc. – Share Price Chart



DISCLOSURES

The following disclosures relate to relationships between Zacks Small-Cap Research ("Zacks SCR"), a division of Zacks Investment Research ("ZIR"), and the issuers covered by the Zacks SCR Analysts in the Small-Cap Universe.

ANALYST DISCLOSURES

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