

## New Product Assessment Warhawk Therapeutic Technologies

Therapeutic proteins are proteins that are either engineered in a laboratory or extracted from human or animal cells for pharmaceutical use as the active substance in a drug. Most of these therapeutic proteins are recombinant human proteins. They are manufactured in non-human mammalian cell lines that have been designed to express a specific human genetic sequence. The majority of these biopharmaceuticals are recombinant therapeutic proteins administered by injection. Once injected into the body, the proteins are broken down by enzymes and cellular activity in the bloodstream and are filtered out of the blood by the body's organs. Thus, patients must receive frequent injections to maintain effective therapeutic levels of protein in the body.

Therapeutic proteins are used for treatment and prevention of diseases and disorders in the human body. For example diabetes, arthritis, infections, heart attacks, and cancers can all be treated through the use of these proteins. There are several production technologies in this industry aimed at maximizing the production yields of these proteins. Current methods of production only yield 10 percent to 20 percent of the therapeutic proteins. However, Warhawk Therapeutic Technologies' production technology is capable of yielding XX – XX percent which, in turn will reduce production costs and initial capital investments on manufacturing facilities. Additionally, the protein folding process employed by Warhawk Therapeutic Technologies does not require the use of strong chemical reagents or special equipment.

The following report includes a review of competition, a preliminary patent search, a sample of market feedback, and an investigation into trends that may affect the market for the Warhawk Therapeutic Technologies protein folding system.

### Existing Technologies

Our competitive analysis uncovered a variety of methods used to produce recombinant therapeutic proteins. These methods include: Chinese Hamster Ovary (CHO) production, Fusion tags, and Microbial expression as well as a few technologies used to increase yields of therapeutic proteins. Our research did not uncover any method or technology that can achieve a production yield of XX-XX percent without the use of strong chemical reagents or special equipment.

### **Recombinant Therapeutic Protein Production Methods**

#### *Chinese Hamster Ovary Production (CHO)*

The majority of recombinant therapeutic proteins marketed today are produced in Chinese Hamster Ovary cells. A handful of other mammalian-based cells including mouse myelomas NS0 and SP2/0, as well as baby hamster kidneys and human embryonic kidney (HEK-293) cells can also be used for production of therapeutic proteins. Nevertheless, CHO cells have proved to be the most effective engine for production. An article published in Chemical Engineering Progress Journal states: "CHO is the dominant force in the biopharmaceutical production market because it represents a cell line that is capable of incorporating the appropriate post-translational modifications while maintaining the characteristics ideal for production

culture. CHO cells are easily maintained in serum-free suspension culture with high viable cell densities and specific protein productivity."

A representative from the U.S. Chapter of the International Biopharmaceuticals Association estimated that CHO cells are responsible for XX percent of all recombinant protein therapeutics produced today. This representative also noted that the yields from CHO cultures have been improving steadily for some time now. While yields can vary widely based on environment, type of protein, etc., the representative said that titers of X g/L of recombinant protein are not uncommon.

Many of the major players in the recombinant therapeutic protein market use CHO cells as a means of treating ailments including arthritis, cancer, asthma, hemophilia and infertility. The manufacturers of recombinant therapeutic proteins via CHO cells include Genzyme, Genentech, Amgen, Bristol-Myers Squibb, Baxter, Serono, Wyeth, BioMarin Pharmaceutical and Abbot Laboratories. Note: This should not be interpreted as an exhaustive list; rather, the companies listed previously make up the majority of manufacturers of FDA approved biologics produced in CHO since 2000.

### *Fusion Tags*

Recombinant fusion proteins can be created through genetic engineering of a fusion gene. Removing the stop codon from a DNA sequence coding for the first protein, and replacing it with a second DNA sequence will result in a different DNA sequence that will be expressed by a cell as a single protein. These fusion tags are typically attached to achieve one or more of the following characteristics: improved solubility, improved detection, improved purification, improved expression, or localization.

WISC contacted a member of the University of Wisconsin's Pharmaceutical Sciences Division to learn about different production methods of recombinant therapeutic proteins. He identified fusion tags, particularly Elastin-Like Polypeptide (ELP) fusion tags, as a technology that holds more promise than other methods. ELPs are responsive to temperatures and undergo reversible aggregation above a certain temperature. This inverse phase transition can be used to purify the fusion proteins from other soluble proteins using nonchromatographic methods termed inverse transition cycling (ITC). The representative from UW Pharmaceutical Sciences said "ITC purification of fusion proteins results in approximately XX percent recovery of active fusion protein." He went on to say that these results are similar to chromatographic purification. Some of the advantages offered by ITC purification and the use of ELP fusion tags are ITC is inexpensive, and requires no specialized equipment or reagents. Furthermore, because ITC is a batch purification process, it can be easily scaled up to accommodate larger culture volumes.

Fusion tags are employed by the following companies to produce purified therapeutic proteins: Genentech, Genzyme, Roche Pharmaceuticals, Bristol Myers Squibb, Stratagene, Pierce Biotechnology, and Santa Cruz Biotechnology,

### *Microbial Expression*

The first recombinant products were produced in *Escherichia coli* over 20 years ago. Today, *E. coli* remains the bacteria of choice for bioengineers using microbial systems. By moving desired genes from one organism to another, scientists can "harvest" the yield of the desired protein. For example, scientists can take the plasmid out of an *E. coli* bacterium, cut the plasmid with a restriction enzyme and splice in the

insulin-producing human DNA. The hybrid plasmid can then be inserted into another *E. coli* bacterium where it multiplies rapidly. Unfortunately, one of the drawbacks to microbial expression is that bacteria often improperly fold complex proteins.

WISC spoke with a representative from the American Association of Pharmaceutical Scientists to discuss microbial systems for producing therapeutic proteins. The representative said “many of the more complex proteins are produced in mammalian cells. Microbial systems are best suited to producing less complex proteins and also have the advantage of reproducing quickly so the volumetric yields are greater.”

Some companies using bacteria to grow therapeutic proteins include: Genentech, Genzyme, Amgen, Bristol Myers Squibb, and Baxter.

### *Other Expression Systems*

Transgenic plants and animals represent a small but important portion of production of recombinant proteins. This technology is capable of producing certain proteins by altering the DNA for either plants or animals to express desired traits. Mice and fruit flies are the primary animals of choice for genetic research. Recently, by targeting the mammary glands of transgenic farm animals, it was determined that transgenic milk production is capable of delivering a cost-effective system for manufacturing large amounts of complex proteins. It is said that transgenic goats can express recombinant human antithrombin at volumes of X g/L. GTC Biotherapeutics and PPL Therapeutics are two companies at the forefront of the research surrounding production of therapeutic proteins via transgenic organisms.

Yeast systems are also being pursued as a means of production of recombinant therapeutic proteins. This method is capable of producing large quantities of proteins (>X g/L) at a lower cost, in a shorter time period, than other mammalian or microbial expressive systems. One major drawback of using yeast as a media is that yeast produce glycosylation patterns different from those in humans, making the resulting proteins liable to malfunction. Several studies have been undertaken to map the glycosylation pattern of yeast, no significant advantages have been accomplished. However, the potential advantages which yeast expression systems may be capable of warrant further investigation. A few companies who are researching yeast systems as a production method include: Baxter, Genentech, and Amgen.

### **Refolding Technologies**

As noted by the client, the patented Pt-Fold Technology employed at **ProteomTech Inc.** (Emeryville, CA; 714-825-0680; [www.proteomtech-inc.com](http://www.proteomtech-inc.com)) is capable of producing therapeutic proteins that are difficult to produce by other methods. Pt-Fold is used for the production of research quantities of recombinant human proteins and for large-scale production of proteins of therapeutic interest. ProteomTech has successfully refolded over XXX recombinant proteins with this technology. The way this technology works is by turning inclusion bodies, which can pose a significant bottleneck in the efficient progression of medical research, into highly-active proteins. The result, high levels of expression for most proteins. Company literature claims production ranges from XXX to XXX mg of inclusion bodies per liter of bacterial culture. Further, inclusion bodies can be easily purified to greater than XX percent purity with a simple freeze-and-thaw and detergent washing procedure. However, it should be noted that ProteomTech is far more versed in *E. coli* expression than mammalian, insect, and yeast cultures. In speaking with a representative at Proteomtech, WISC learned that Proteomtech has used their refolding technology, on a

contract basis, with “over XX companies worldwide, including some of the big players in the pharmaceutical industry.” The representatives declined to disclose specific companies.

Also noted by the client, **Barofold Inc.** (Boulder, CO; 303-926-0337; [www.barofold.com](http://www.barofold.com)) has developed and patented a protein processing technology that uses hydrostatic pressure to disaggregate and refold recombinant proteins. This technology is called PreEMT and in this system, aggregated protein is exposed to elevated pressure dissolving aggregates. The high fluid pressure unwinds biotech-drug proteins that have stuck together and forces proteins that have folded incorrectly to unfold and refold into a proper configuration. Biologically active, native proteins are recovered within hours at yields of up to XXX percent. This process has been tested and proven successful on over XXX proteins. Barofold has documented volumetric yields of recombinant human growth hormone equaling XX g/L with a yield of XXX percent. Additionally, the PreEMT technology is scalable using commercially available equipment used in the food and chemical industries which allows for greater cost savings than other methods. In 2008, Barofold Inc. received the “Biosciences Company of the Year” award. The “Biosciences Company of the Year” award recognizes inventors, companies, and community leaders who demonstrate best practices in technology transfer. Barofold has granted research licenses to companies such as Genentech, Pfizer, and Eli Lilly.

**Expedeon** (Cambridge, UK; +44 1223 496744; [www.expedeon.com](http://www.expedeon.com)) has developed a proprietary method used to refold proteins. This system, called NVoy, protects and stabilizes proteins against aggregation enabling the processing of difficult to handle proteins at high concentrations under conditions that would usually result in the formation of useless aggregates. Company literature claims that the use of NVoy offers an alternative to the use of “detergents, fusion proteins, chaperones and the myriad of other techniques employed to overcome common problems faced when working with proteins, enzymes and antibodies in solution.”

## Preliminary Patent Search

As part of our competitive assessment, WISC also conducted a preliminary patent search for additional competition. We found a few patents that appear to offer some related benefits.

**U.S. Patent # 6,583,268** (issued: June 24, 2003; assigned to Oklahoma Medical Research Foundation of Oklahoma City, OK) is for a “Universal Procedure for Refolding Recombinant Proteins.” The patent abstract states:

“A universal folding method that has been demonstrated to be effective in refolding a variety of very different proteins expressed in bacteria as inclusion bodies has been developed. Representative proteins that can be dissolved and refolded in biologically active form, with the native structure, are shown in Table I. The method has two key steps to unfold and then refold the proteins expressed in the inclusion bodies. The first step is to raise the pH of the protein solution in the presence of denaturing agents to pH greater than 9, preferably 10. The protein solution may be maintained at the elevated pH for a period of up to about 24 hours, or the pH immediately decreased slowly, in increments of about 0.2 pH units/24 hours, until the solution reaches a pH of about 8.0, or both steps used. In the preferred embodiment, purified inclusion bodies are dissolved in 8 M urea, 0.1 M Tris, 1 mM glycine, 1 mM EDTA, 10 mM beta-mercaptoethanol, 10 mM dithiothreitol (DTT), 1 mM

reduced glutathion (GSH), 0.1 mM oxidized glutathion (GSSG), pH 10. The absorbance at 280 nm (OD280) of the protein solution is 5.0. This solution is rapidly diluted into 20 volumes of 20 mM Tris base. The resulting solution is adjusted to pH 9.0 with 1 M HCl and is kept at 4° C. for 24 hr. The pH is adjusted to pH 8.8 and the solution is kept at 4° C. for another 24 hrs. This process is repeated until the pH is adjusted to 8.0. After 24 hr at pH 8.0, the refolded proteins can be concentrated by ultrafiltration and applied to a gel filtration column for purification.”

**U.S. Patent # 7,064,192** (issued: June 20, 2006; assigned to The Regents of the University of Colorado-Boulder, CO) is for a “High Pressure Refolding of Protein Aggregates and Inclusion Bodies.” The patent abstract states:

“The present disclosure provides an effective method for the refolding of denatured proteins in solution so that properly folded, biologically active protein in solution is recovered in high yield. The refolding takes place at pressures between about 0.25 kbar to about 3.5 kbar, advantageously at about 1.5 kbar to about 3 kbar. Typically a chaotropic agent is present at a concentration which is not effective for denaturing protein at atmospheric pressure, and optionally, oxidation-reduction reagents can be incorporated in the refolding solution so that native intramolecular disulfide bonds can be formed where that is desired. The method is applicable to substantially all proteins, especially after solubilization and/or denaturation of insoluble protein aggregates, inclusion bodies, or abnormal oligomeric (soluble) aggregates.”

**U.S. Patent Application #2008/0200665** (application date: August 21, 2008; unassigned) is for a “Nucleic Acid Molecules Encoding Proteins Which Impart the Adhesion of Neisseria Cells to Human Cells.” The patent application’s abstract states:

“Described are nucleic acid molecules encoding proteins mediating the adhesion of bacteria of the genus *Neisseria* to human cells. Also described are the proteins encoded by these nucleic acid molecules and antibodies directed against them. Furthermore, pharmaceutical compositions, vaccines and diagnostic compositions containing the nucleic acid molecules, proteins and/or antibodies are described.”

**U.S. Patent #7,417,178** (issued August 26, 2008; assigned to Ventria Bioscience of Sacramento, CA) is for an “Expression of Human Milk Proteins in Transgenic Plants.” The patent abstract states:

“The invention is directed to seed and seed extract compositions containing levels of a human milk protein between 3-40% or higher of the total protein weight of the soluble protein extractable from the seed. Also disclosed is a method of producing the seed with high levels of extractable human milk protein. The method includes transforming a monocotyledonous plant with a chimeric gene having a protein-coding sequence encoding a protein normally present in human milk under the control of a seed maturation-specific promoter. The method may further include a leader DNA sequence encoding a monocot seed-specific transit sequence capable to target a linked milk protein to a storage body.”

Ventria Bioscience products related to this patent have not been disclosed to date.

**U.S. Patent Application #2008/0207644** (application date: August 28, 2008; unassigned) is for "Therapeutic Materials and Methods." The patent abstract states:

"Disclosed are methods for treating various cancers. Methods encompass the administration of an mTOR inhibitor in combination with a second drug selected from an ImiD, a PDE4 inhibitor, a p38 MAP kinase inhibitor, a xanthine anticytokine, a dual TACE/MMP inhibitor and a proteasome inhibitor. The methods are aimed at providing a desirable therapeutic window while maintaining prior, if not higher, dose levels of the mTOR inhibitor"

**U.S. Patent Application #2008/0207886** (application date: August 28, 2008; unassigned) is for a "Mammalian Cytokine-like Polypeptide-10." The patent abstract states:

"A mammalian cytokine-like polypeptide, called Mammalian Cytokine-like polypeptide-10, (Zcyto10), polynucleotides encoding the same, antibodies which specifically bind to the polypeptide, and anti-idiotypic antibodies which bind to the antibodies. Zcyto10 is useful for promoting the healing of wounds and for stimulating the proliferation of platelets."

## **Market Need and Relevant Trends**

We spoke with a few industry representatives about market need for products of this type and also investigated trends that may affect the demand for a higher yielding method of producing therapeutic proteins. Trends include the current biopharmaceutical capacity crunch, increases in volumetric yields, extending protein lifespan, approval trends, and chronic disease rates in the U.S.

### **Market Need for a Higher Yielding Therapeutic Protein Folding System**

#### *The Therapeutic Protein Market*

A research report published by Business Insights, titled "Next Generation Protein Engineering and Drug Design" details the rapid growth this market is currently experiencing. The therapeutic protein market was worth approximately \$XX billion in 2006, and accounted for an estimated XX percent of all pharma sales. Both of these estimates are projected to rise to \$XXX billion and XX percent, respectively, by 2011. This growth is said to be fueled by sales of erythropoietin (EPO) and insulin used to treat anemia and diabetes, respectively ([www.marketresearch.com](http://www.marketresearch.com); 2007).

Currently, the majority of products on the therapeutic protein market is immediate-release and largely introduced to the body via injection. However, research published by *Datamonitor* suggests that an emerging trend in this competitive environment is moving more toward sustained release formulations. Additionally, non-injectable solutions to the delivery of therapeutic proteins are increasingly being evaluated, a trend that is expected to accelerate ([www.datamonitor.com](http://www.datamonitor.com); March, 2005).

WISC spoke with a member of the Pharmaceutical Sciences Division at the University of Wisconsin to gain better insight into this market. He said that this market is "extremely competitive" and noted that two companies, Genentech and Genzyme, dominate this market. However, he said that because this market is experiencing such robust growth, there may be an opportunity for expansion for more small- to medium-sized startup companies. He also noted that the barriers to entry are relatively high owing in large part to

expensive start-up costs and the experience requirements needed to compete effectively. Owing to these high barriers to entry, he said that it is common for small- to medium-sized companies to merge with larger companies in this industry. This representative also felt that a production method capable of yielding XX percent to XX percent of the purified proteins, representing an xx- or xx-fold increase in yield, would be a significant improvement over current production methods.

WISC also asked what some of the obstacles were that new entrants into this market would have to overcome. His response revolved around three major hurdles. First was the competitive environment of the biopharmaceutical market. Large established companies such as Genentech and Genzyme have the production capabilities to squeeze out (or acquire) new entrants. Second, new entrants and technologies must show that the bioactivity of their recombinant protein is stable over time. Finally, the representative listed the high cost of these drugs as a potential obstacle because many HMOs are reluctant to cover such expensive treatments.

## Relevant Trends

### *Capacity Crunch*

WISC spoke with a representative from Biopharmaceutical Research Inc. about trends affecting the market for biopharmaceuticals. He emphasized the significance of the capacity crunch: "There is no doubt that there is more money to be made in biopharma. The demand for therapeutic proteins is currently outpacing the supply.....The reasons for the shortfall in supply are associated with the length of time it takes to design, build, and certify new plants, and the large capital requirements associated with developing a drug." The representative also said that one strategy for increasing supply of these proteins is by working to increase volumetric yields, particularly with the vast number of recombinant proteins currently in clinical trials.

### *Increases in Volumetric Yields*

An article published in *BioPharm International Supplements* describes the increases in volumetric yields experienced by recombinant therapeutic proteins grown in mammalian cells. In 1986, the industry standard for production from stable Chinese Hamster Ovary (CHO)-derived cell lines was XX pg protein/cell/day, with volumetric yields of XX mg/liter for batch processes that lasted up to a week. By 2004, the highest reported specific and volumetric productivities were up to XX pg/cell/day and X g/L for an extended batch culture lasting up to three weeks. However, the reasons pertaining to how these advances have been achieved are not entirely known because manufacturers are reluctant to reveal their insights into the production of recombinant cell lines. According to the article, it is clear that four factors have contributed to the overall improvement in yields: the generation of recombinant cell lines with high specific productivities; the formulation of media to support high-density cell cultivation; the understanding of bioprocess conditions for cell cultivation; and the sustained viability of cell lines in high-density batch and extended batch cultures (BioPharm International Supplements; June 2008).

### *Extending Protein Lifespan*

Recombinant proteins typically have short effective lives in the bloodstream. As such, patients requiring these proteins for their therapeutic value need to have frequent injections. Many of the drugs that

gain approval in any given year are simply alterations to extend the lifespan of previously approved pharmaceuticals. According to our research, a total of four treatments exist that aim to extend the effective lifecycle of therapeutic proteins (Crystal Research Associates; August 2007).

Bolus injections attempt to counteract a protein's short half-life (to roughly XX hours at optimal therapeutic levels) by introducing a temporary overdose of the treatment to the patient's bloodstream. However, bolus injections are likely to cause unwanted side effects such as hypertension and stroke. Another method of extending a protein's lifespan is by attaching polyethylene glycol (PEG) molecules to the protein. This effectively lengthens the time a substance remains in the bloodstream without being metabolized. Many PEGylation attempts to date have failed for therapeutic proteins, but three companies—Schering Plough Corp., Roche Holdings, and Amgen—have successfully developed such proteins that boast longer lifecycles than their original counterparts (Crystal Research Associates; August 2007)

Glycosylation is the process of adding sugar molecules to proteins. The sugars add carbohydrate structures to the protein's genetic sequence, increasing the protein's lifespan by slowing the clearance of the protein from the bloodstream. However, because the structure of the protein is altered, adverse, and potentially toxic side effects, can occur. One successful protein that has additional glycosylation sites is Amgen's Aranesp, which utilizes a longer-lasting version of EPO to treat various forms of anemia (Crystal Research Associates; August 2007).

Finally, protein fusion technology creates new proteins by fusing the genes for large human proteins that are capable of circulating in the body for long periods of time, to the gene that encodes the active protein drug. Because the new proteins are significantly larger than their previous structure, one drawback may be that the binding sites may be compromised, resulting in loss of activity. Human Genome Sciences Inc. has successfully fused albumin to interferon- $\alpha$ . With the resulting molecule, Albuferon, the company has obtained approval to initiate Phase III clinical trials as a potential treatment once every two weeks for chronic hepatitis C. Human Genome Sciences has also fused hGH to albumin (Albutropin); however, the development of this product has been put on hold for undisclosed reasons (Crystal Research Associates; August 2007)

### *Approval Trends*

An article published in Nature Biotechnology of 2006 details some approval trends which biopharmaceuticals have encountered. Since 2003, a total of XX biopharmaceuticals have been approved for human use by North American and European regulatory bodies. These drugs included recombinant hormones and growth factors, mAb-based products, and therapeutic enzymes, as well as one recombinant blood factor, two recombinant vaccines, and a nucleic acid-based product. Although the products approved represent very significant product categories, no interferon, interleukin, thrombolytic, or anticoagulant-based biopharmaceutical was approved over the past three years, and only two recombinant vaccines and one recombinant blood factor came on the market. The article goes on to say that these trends most likely reflect commercial rather than technical considerations. For example, new interferons, thrombolytics, or blood factors would likely face stiffer competition as numerous products treating such categories are already on the market (Nature Biotechnology – 2006)

In 2007, only XX new drugs were approved by the Food and Drug Administration (FDA). This represents one of the slowest years for new drug approvals to date. However, *Pharmalot* reports new



analysis indicating XX new drug approvals through April of 2008, the fastest rate of acceptance since 1998 and 2000. It should be noted that XX of the XX new approvals are for therapies that build on existing drugs. A total of X new molecular entities (NME) were approved for this period. One healthcare analyst at Friedman Billings Ramsey had this to say about NME approvals:

“We view NME approval trends as a more critical metric than overall new drug approval trends because NMEs represent novel compounds carving out entirely new pharmaceutical niches. These are the compounds that break new clinical ground and require the most effort in educating physicians, patients, and payers” (Pharmalot; May 2008)

A different article published in the *The Boston Globe* from August of 2008 says that U.S. marketing applications for drug candidates made with NMEs increased XX percent in 2007. So it is expected that the number of NMEs coming to market should rise in the upcoming years. Global launches for NMEs declined in 2007 but marketing applications for NMEs increased substantially, according the U.S. Drug Approval Trends and Yearbook 2008/2009 (*The Boston Globe*; August, 2008).

### *Chronic Diseases in the U.S.*

One of the main purposes of therapeutic proteins deals with treating chronic diseases. As such this market is directly affected by the growth rate of chronic disease. Experts attribute the rising prevalence of chronic disease to a large aging population and to increasing rates of obesity. The percentage of obese adults has more than doubled in the last 30 years—from XX.X percent to XX.X percent as of 2004. As a result, the prevalence of diabetes has doubled in the U.S. between 1994 and 2004. As obesity rates increase and the population ages, the prevalence of those suffering from preventable chronic diseases will likewise increase. One estimate says that as the proportion of the population aged 65 years or older is projected to grow from XX percent in 2000 to XX percent in 2030, the number of people with a chronic disease is expected to grow by XX percent to reach XX million more people (PhRMA – 2008).

## **Conclusion**

In terms of competition, a number of alternatives exist in the production of recombinant therapeutic proteins. They are mammalian expression such as Chinese Hamster Ovaries (CHO), fusion tags, microbial expression, and other expression systems such as transgenic plants and animals, or yeast systems. Primary and secondary research both suggest that CHO continues to be the industry standard for production of complex therapeutic proteins. E. coli cultures have also proven to be effective at producing large quantities of therapeutic proteins. Other forms of competition include refolding technologies such as those employed by ProteomTech Inc., Barofold Inc., and Expedeon.

Trends which may affect the market for the Warhawk Therapeutic Technologies system appear to be favorable. The market for therapeutic proteins is experiencing strong growth. In fact, the demand for these treatments is currently outpacing supply. Therefore, significant room for expansion either from companies already established in this market or from new startups is ample. One reason there is such a gap between supply and demand has to do with the capacity crunch that the biopharmaceutical market is experiencing. The length of time it takes to design, build, and certify new plants, and the large capital requirements associated with developing a drug, were cited as the primary causes of the crunch. One strategy for increasing the supply of therapeutic proteins is to increase volumetric yields. Yields of purified

therapeutic proteins have been increasing steadily over the past decade owing to the following four reasons: the generation of recombinant cell lines with high specific productivities; the formulation of media to support high-density cell cultivation; the understanding of bioprocess conditions for cell cultivation and the sustained viability of cell lines in high-density batch; and extended batch cultures. Another strategy to alleviate the capacity crunch on the biopharmaceuticals market is to extend the lifespan of recombinant therapeutic proteins. Currently, these proteins must be administered to the patient by frequent injections. Studies are underway that look to extend the lifespan of therapeutic proteins in the body so fewer injections will be needed.

Other trends that may affect the market for the Warhawk Therapeutic Technologies system include fluctuations in the number of approvals granted by the FDA and EMEA for new biopharmaceuticals. Last year marked one of the slowest periods of approval in recent history when only XX new treatments were approved. However, this seems to be turning around for 2008, because as of April, XX new approvals have been granted. This represents the fastest rate of approval since 1998. It should be noted that only X of these new approvals are for NMEs. Finally, given the prevalence of chronic diseases in the U.S., there will be additional need for therapeutic proteins in the future.

Overall, Warhawk Therapeutic Technologies appears to be both a useful and feasible system which could improve upon existing technologies in the production of recombinant therapeutic proteins. Although our research did identify a few competitive technologies already on the market, given the growth this market is experiencing, as well as the capacity crunch it is currently enduring, it appears that the market could support another recombinant therapeutic protein production method. However, owing to the high barriers to entry (large capital requirements, experience factors, etc.) WISC would recommend that the client further explore licensing options with one of the larger biopharmaceutical companies that is already established in this market.

## Research Notes

The following companies or organizations were cited in the report:

<u>Company</u>	<u>Location</u>	<u>Phone Number</u>	<u>Web Site (http://www.)</u>
UW School of Pharmacy	Madison, WI	608-262-0353	pharmacy.wisc.edu
Biopharm. Researchl	Vancouver, BC	604-432-9237	biopharm.com
AAPS	Arlington, VA	703 243 2800	aapspharmaceutica.com
Proteomtech Inc.	Emeryville, CA	714-825-0680	proteomtech-inc.com
Barofold Inc.	Boulder, CO	303-926-0337	barofold.com

The following companies or organizations were contacted but did not provide information for this report:

<u>Company</u>	<u>Location</u>	<u>Phone Number</u>	<u>Web Site (http://www.)</u>
Ctr for Pharm. Research	Kansas City, MO	816-943-0770	cprkc.com
PhRMA	Washington, D.C.	202-835-3400	phrma.org
NIGMS	Bethesda, MD	301-496-7301	ngims.nih.gov
Expedeon	Cambridge, UK	+44 1223 496744	expedeon.com
OK Med. Research Fd.	Oklahoma City, OK	405-271-6673	omrf.org
Ventria Biosciences	Sacramento, CA	916-921-6148	ventria.com
Genentech Inc.	San Francisco, CA	650-225-1000	gene.com
Genzyme Corp.	Cambridge, MA	617-252-7500	genzyme.com

## **Patent Search**

The following patents appear to be related to the client's proposed device. The full texts and illustrations of these patents are available at [www.uspto.gov](http://www.uspto.gov).

<u>U.S. Patent #</u>	<u>Description</u>
7,417,178	Expression of Human Milk Proteins in Transgenic Plants

## Published Research Reports

Business Insights, "Next Generation Protein Engineering and Drug Design", published February 1, 2007  
Publication ID: RET1466998; Available for download at [www.marketresearch.com](http://www.marketresearch.com); US\$2,875

DataMonitor, "Protein Drug Delivery, Penetrating a Growth Market", published March 2005  
Publication ID: DMHC2036; Available for download at [www.datamonitor.com](http://www.datamonitor.com); Consult Website for current pricing