Development of a Business Plan for a Recombinant DNA Technology Based Pharmaceutical Company

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Abstract

This master's thesis establishes a business plan for the formation of a pharmaceutical research and development company. The Company's products are based on recombinant DNA and monoclonal antibody technology and initially addresses the infectious disease market. The Company as initially set up, will conduct contract research and development. It will enter into joint ventures or license its products for manufacture and marketing. The Company may decide at a later date to manufacture and market its own products.

The thesis analyzes the Company, the pharmaceutical industry, the Company's products and its entry and growth strategy. It presents the results of a market research analysis of potential customers, market size and trends, competition and estimated market share and sales. It also presents a design and development plan, manufacturing plan, marketing plan, financial plan and analyzes the critical risks and technological decisions of the venture.

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Glossary

Allotype-- the genetically determined antigenic differences in the same class of proteins in the same species, i.e., differing amino acids in the same region of an IgG antibody molecule between two people.

Anti-allotypic antibody-- an antibody which has its antigen binding site directed towards an allotype.

Anti-idiotypic antibody-- an antibody which is directed to the variable region of a second antibody.

Antibiotic-- any of various substances that are effective in inhibiting the growth of or destroying microorganisms, widely used in the treatment and prevention of disease.

Antibiotic resistence-- a term used for bacteria which, through various mechanisms, are no longer killed by a particular antibiotic.

Antibiotic resistence gene-- the DNA segment, or gene, responsible for providing the bacteria with the antibiotic resistance.

Antibody (Ab)-- proteins which are generated in response to foreign proteins or polysaccharides (antigens), neutralize them, and thus produce immunity against them.

Antibody-mediated protection-- a form of the immune response using antibodies as a mediator in the destruction of a pathogenic microorganism or particle.

Antigen (Ag)-- any substance that, when introduced into the body, stimulates the production of antibodies.

Avidity-- the degree of chemical or physical attractive force between two substances.

Bacterial transformation-- the introduction of new genetic information into a bacterial cell using a segment of DNA.

Bioprocessing-- any process that uses complete living cells or their components (i.e., enzymes) to effect desired physical or chemical changes.

Bioreactor-- apparatus in which bioconversions take place.

Glossary (continued)

Biotechnology-- commercial techniques that use living organisms, or substances from those organisms, to make or modify a product.

Cell line-- cells that acquire the ability to multipy indefinitely *in vitro*.

Chimaera-- a name for any new organism or hybrid molecule produced by genetic engineering.

Chimaeric antibody-- an antibody made through genetic engineering containing parts from different species (i.e., human/murine).

Cloning-- the isolation and amplification of a particular gene (DNA segment).

Complement protein-- proteins in the blood which are the primary mediator of antigen-antibody reactions.

DNA--deoxyribonucleic acid-- the basic biochemical component of the chromosomes and the support of heredity.

DNA probe technology-- technology that uses a sequence of DNA to detect the presence of a similar piece of DNA in a sample.

EBV-- Epstein-Barr virus.

Expression-- the mechanism by which genetic information is transcribed and translated to obtain a protein.

Extrachromosomal-- existing separate from the cell's normal chromosomes.

Fermentation-- any chemical reaction induced by living organisms (yeast, bacteria) or chemical agents (enzymes) which converts complex organic molecules into relatively simple substances.

Fusion (cell)-- formation of a single hybrid cell with nuclei and cytoplasm from different cells.

Gamma globulin-- the fraction of blood which contains the majority of antibodies and immunoglobulins.

Gene-- the basic unit of heredity, which plays a part in the expression of a particular characteristic.

Glossary (continued)

Genetic engineering-- the technique used to modify the genetic information in a cell, reprogramming it for a desired purpose.

Hybridoma-- hybrid cell made by fusing a cancer cell ("immortal") with a lymphocyte (antibody producing cell).

Idiotype-- the antigenic site of an antibody molecule, located in its variable region.

Immunity-- the condition of being immune or resistant.

Immunocompromised-- the state in which one's immune system is not working to its normal capacity.

Immunoglobulin (Ig)-- a glycoprotein that functions as antibody. All antibodies are immunoglobulins.

In vitro--in an artifical environment outside the living organism; in a test tube or plastic growth flask.

In vivo-- within the living organism.

In vivo imaging-- using labelled antibodies to identify the location of a tumor or site of infection within the body.

Mammalian cell line-- cell line derived from mammals (human, monkey).

Monoclonal antibody (mAb)-- highly specific antibody derived from a single cell source.

Murine-- mouse.

Natural immunity-- the presence of antibodies in the serum of an individual in the absence of apparent antigenic contact.

Nosocomial-- any infection or disease acquired at a hospital.

Opportunistic pathogen-- a potential pathogen (bacteria) normally present in the environment, that takes advantage of an immunodeficient host.

Passive immunization-- immunization accomplished by passively administering preformaed immunoglobulins (Ab's) to the host's own immune system.

Passive immunotherapy-- the act of passive immunization.

Pathogen-- a specific causative agent (as a bacterium or virus) of disease.

Plasmid-- an extrachromosomal, self-replicating, circular segment of DNA.

Polyclonal Antibodies-- a mixture of antibodies derived from many different cells, each with different binding targets.

Prophylaxis-- measures designed to preserve health.

Prophylactic-- guarding from or preventing disease.

Protective antibody-- an antibody that can be used to prevent or protect against the damage to the host, from an invading microorganism.

Recombinant antibody (rAb)-- the use of recombinant DNA techniques to produce a functional antibody molecule.

Recombinant DNA (rDNA)-- the hybrid DNA produced by joining pieces of DNA from different organisms or the same organisms together <u>in vitro</u>.

Recombinant DNA technology-- the use of rDNA for a specific purpose, such as the formation of a new gene product or the study of a gene.

Restriction enzyme-- bacterial enzymes that cut DNA at specific DNA sequences.

Superinfection-- reinfection or a second infection with the same type of microbial agent (bacteria, fungus, virus).

Transformed cell line-- a cell line that is immortal; it has the ability to form a tumor when injected into mice.

Viral particles-- particles of virus' made from a virally infected cell.

Viral transformation-- the introduction of viral genetic information into a cell.

The Business Plan

I. Executive Summary

The management believes there is a significant opportunity in the infectious disease market. The Company will be addressing new product development, i.e. ethical pharmaceuticals, that will be used to kill bacterial pathogens. The targeted markets are those in which their is either little effective therapy or no present therapy available.

I.A. Description of the Business

The Company will be in the business of producing ethical pharmaceuticals. The Company is a zero-stage recombinant DNA technology based, pharmaceutical development company. It will develop therapeutic and prophylactic recombinant antibodies (rAb's) for various infectious disease bacterial pathogens. Initially, the Company will not manufacture or market it's own products. For manufacturing and marketing it will enter into contractual R&D arrangements with established pharmaceutical companies. The Company will initially become a drug development company, providing key health care components to established pharmaceutical companies, with options to later develop into an integrated pharmaceutical company.

I.B. The Opportunity and Strategy

In the U.S., approximately 10 million individuals per year require hospitalization for bacterial infections. An additional two million acquire bacterial infections once in the hospital. Furthermore, a large number of hospitalized

immunocompromised and immunodeficient individuals are "at risk" for bacterial infection. Although great advances have been made in antimicrobial therapy, i.e., antibiotics, bacterial resistance remains an increasingly serious problem. Bacteria continue to evolve new mechanisms of resistance to new and old antimicrobial agents found in nature or those synthesized by organic chemists.

An individual's natural defense against bacterial pathogens involves a complex immune response. Antibodies play a major role in this defense system. An infected, immunocompromised or immunodeficient individual does not always possess the proper protective anti-bacterial antibody. Further, an individual may not always undergo the induction of protective anti-bacterial antibodies. An alternative or adjunct to both natural immunity and antibiotic therapy is the use of passive immunization with preformed antibodies. Along these lines, man has been using immune serum globulin preparations for almost 100 years. These preparations, derived from pooled sera from thousands of naturally immunized individuals, usually contain minute quantities of the protective antibody of interest and are difficult to quality control. A source of pure bacterial specific human antibody could solve these problems and ultimately circumvent the problems and use of antibiotics.

Human monoclonal and recombinant antibodies provide a novel approach to new drug development for bacterial pathogens. Such antibodies can be pre-selected for specific bacteria and can be made <u>in vitro</u> in unlimited quantities. However, progress in human monoclonal antibody (mAb) production (for use as ethical pharmaceuticals) has been slow. <u>Recombinant antibodies</u> circumvent the problems associated with human monoclonal antibody production and additionally add the potential of producing hybrid antibodies. Recombinant antibodies also circumvent the

bacterial resistance problem. The potential of recombinant antibodies alone or as an adjunct to more conventional antibiotic therapy appears great. The realization of this potential is one which is more economic than scientific.

Quick entry into this field will be pursued by first licensing monoclonal antibodies from university labs and then converting them into recombinant antibodies for therapeutic and prophylactic use as ethical pharmaceuticals. The Company will shortly thereafter begin development of its own in-house monoclonal antibodies, for recombinant antibody conversion. The technology offers a good deal of both economies of scale and scope. Using the same technology (rAb production), the Company can later expand its product targets to cover a wide range of uses including the following:

- rAb's for use as drugs against other pathogenic microorganisms (bacteria, fungi, virus, yeast)
- use in targeting toxic compounds and other molecules to specific cells
- use in *in vivo* imaging
- use in industrial purification.

I.C. The Target Market and Projections

The initial market opportunities being addressed are for the following bacterial pathogens: *Pseudomonas aeruginosa*, *Haemophilus influenzae* type b, *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Escherichia coli*, *Klebsiella* and *Salmonella*. These bacterial disease candidates provide good initial targets for recombinant antibody therapy as they cause significant numbers of new cases each year, exhibit drug resistance and for which effective vaccines are not available.

Total market values for drugs used against these bacterial pathogens are approximately $423 million, $226 million, $82 million, $78 million, $178 million, $63 million and $80 million, respectively. These values include the U.S., U.K., France and Germany only. These seven product targets represent in total approximately $1.13 billion dollars. These values are very conservative estimates, using pricing strategies that will be competitive with current antibiotic therapy. In several cases there is no competitive antibiotic therapy and higher prices can be established. The Company's products will not come into the market until seven years from its inception, at the earliest. This is due to the extensive governmental regulatory requirements necessarey for use of drugs in humans. The Company's products will be sold directly to pharmacies (local, government and hospital).

I.D. The Competitive Advantages

The competitive advantages of the Company lies in its product focus, innovative products addressing markets where current therapy is ineffective or unavailable, and its highly "skilled-in-the-art" scientists. Almost all of the Company's potential competitors are focusing on either antibody diagnostics or therapeutics for cancer. Many are also focusing on diagnostic antibodies for use in infectious disease. The use of monoclonal or recombinant antibodies as a therapeutic modality is in its infancy.

I.E. The Economics of the Business

The Company expects to receive revenues in its second year from contract R&D. Profitability lies in the success of low cost manufacturing and pricing strategies. Depending on the contracts reached, the Company could operate at break even in its second year. Based on 80% gross margins, $100/dose treatment and 10% royalties on product sales, the Company is highly profitable. Over the twelve year time horizon analyzed in this plan, the Company would have an estimated before tax net present value of $105.00 million.

II. The Industry

II. A. The Pharmaceutical Industry

II.A.1. Specifics to the Company: Current Status

The industry in which the proposed business will operate is the human healthcare/pharmaceutical industry. Specifically, in the first stage of development, the Company will focus on the infectious disease segment of the pharmaceutical industry. Approximately 25 percent of all the 40 million hospital admissions (10 million) are due to community acquired infections, those obtained outside of the hospital (1,2). Bacterial infections rank among the top ten leading causes of death in the U.S. Alarmingly, five percent or two million of the 40 million patients that enter hospitals annually acquire infections during their stay (1). These are patients who enter the hospital for an altogether different reason, and yet six percent or 120,000 of them die due to hospital acquired pathogenic microorganisms, primarily bacteria (2,3). In addition, over 50 percent of all hospitalized patients are "at risk" for bacterial infections.

Current therapy in fighting infectious pathogenic bacteria involves treatment of infected patients with antibiotics. In treating infections there are usually several antibiotic choices, varying in efficacy. However, pathogenic bacteria are notorious for consistently developing antibiotic drug resistance (4-9). Despite the advent of potent antibiotics and aggressive support techniques, deaths from infectious pathogenic bacteria continue to occur at a high frequency (10). As a result, mortality rates have been increasing.

Additional problems have occurred with the use of antibiotics. Physicians often prescribe a combination

antibiotic therapy (11). One reason for this is that searching for the unknown site or cause of a particular infection is more difficult and time consuming than simply adding additional antibiotics to the treatment regimen and hoping that the patient recovers. In addition to cost, potential health problems can arise. These include: a) potential for disruption of the natural flora in the body, b) increased frequency of superinfection, c) greater likelihood of adverse drug reactions, d) need for more careful monitoring of adverse reactions, e) antagonism between the two antibiotics at the site of infection, f) competition in and change in drug elimination routes through the body and g) many people have allergic reactions to antibiotics. As a result, drug companies are continually searching for new and improved antibiotics, in addition to entirely new and different therapeutic drugs.

An alternative, in some cases, to antibiotic therapy has been the use of gamma-globulin injections for the treatment of infectious disease (12). The gamma-globulin preparations represent pooled sera from thousands of healthy individual donors, containing polyclonal antibodies (see technical background). This form of treatment is referred to as passive immunization. The major problems with gamma-globulin preparations are that they are often contaminated with unwanted compounds, activate unwanted natural immune responses, are highly non-specific and are in limited supply. Companies have tried to deal with the first two problems, with some degree of success (13). However, the last two problems have not been overcome using this methodology. The historical imperative of human immune gamma globulin as a therapeutic modality argues strongly for the potential of <u>human monoclonal antibodies</u> and <u>recombinant antibodies</u> (defined below) (13,14).

II.A.2. The "New" Biotechnologies

Biotechnology is a generic term for a group of technologies including existing bioprocessing, fermentation technology and the relatively "new" technologies such as recombinant DNA (genetic engineering) and antibody/hybridoma technology. Broadly defined, the term biotechnology includes any technology that uses living organisms to make or modify products. The applications of biotechnology are very broad and involve pharmaceuticals, agriculture, specialty chemicals and food additives, commodity chemicals and energy products, environmental applications and bioelectronics.

In the past 15 years there has been a revolution in molecular biology and in our knowledge of biological systems. The following discoveries have led to the development of powerful new techniques with industrial applications:

(1) Antibiotic resistance genes in bacteria were found to be maintained on DNA elements called plasmids.

(2) Bacteria gain immunity from viruses through the use of their restriction enzymes which destroy the viral DNA.

(3) Foreign DNA can be inserted into bacteria, a process referred to as bacterial transformation.

(4) Monoclonal antibodies (specific for a single antigen) can be produced through hybridoma technology.

These discoveries have led to the isolation, molecular cloning and expression (in bacteria and mammalian cells) of individual human genes. This is quite useful as it provides an unlimited supply of therapeutic drugs, many of which are new and never before available.

The commercial significance of these discoveries was first realized when new companies like Cetus Corporation (Berkeley,CA. 1971) and Genentech, Inc. (S.S.F.,CA., 1976) were formed to exploit the new technologies. Many start-up biotechnology based companies followed from 1976 to the present, and since 1979/1980, many large, established pharmaceutical, chemical, food and oil companies have invested in this new area of research and development (R&D) called biotechnology (15).

The "new" biotechnologies bring with them new R&D approaches for companies in developing new products. These technologies enable advancement in basic research in such areas as cellular and molecular biology and biomolecular structures that elucidate disease processes and provide clues to help molecular biologists, organic and protein chemists in designing molecular entities having therapeutic properties. These new "targeted" rather than the conventional "shot-gun" approaches to drug development have the potential of producing significant advances in medical research and therapy (16).

Through the advent and proliferation of monoclonal antibody (mAb) production and recombinant DNA technology, the "new" biotechnologies, it is now possible to use our body's own natural disease fighting agents, antibodies, in fighting bacterial infections (17,18).

II.A.3. New Product Developments: Recombinant Antibodies

Using the "new" biotechnologies, recombinant DNA and monoclonal antibody technologies, there is the possibility of new product development in the treatment and prevention of infectious disease. Monoclonal and recombinant antibodies can be used instead of the microbially produced antibiotics, or crude gamma-globulin

preparations, in fighting bacterial infections. The advantage of antibodies over the use of antibiotics are that bacteria do not become resistant to them.

Monoclonal antibody technology has already brought a number of notable advantages in our knowledge of the causative agents in infectious disease at the molecular level. However, the use of mAb's for prophylaxis and therapy of bacterial infections is in its infancy. Until the advent of mAb production, antibodies for therapeutic and prophylactic applications have been obtained as impure mixtures (gamma globulin), containing thousands of antibodies, called polyclonal antibodies, with the antibody of interest representing a very small proportion. These preparations were largely from animal and human blood (gamma-globulin preparations). While being similar to the body's own disease fighting weapons, the mAb's are often of non-human origin, usually rodent (mouse). As a result they are not well tolerated by the human body and become rejected as foreign tissue. Therefore, at the present state of development, mAb's are of limited value in fighting disease. (However, mAb's are extremely valuable reagents for diagnostic tests). What is needed for the prevention of infection in high risk patients is a continuous and well characterized (with respect to physical and chemical properties, production and efficacy) source of <u>human</u> mAb's. A major barrier to their therapeutic use has been the inability to produce mAb's of human origin with pharmaceutical standards of quality (see page). Currently, human mAb's are produced largely by viral transformation of human producing antibody cells. Antibodies produced in virally transformed cell lines have not met FDA guidelines for the production of therapeutic drugs. The primary advantage in obtaining human mAb's comes when passive immunotherapy is being considered.

Recombinant antibodies (rAb's) offer many advantages over conventional polyclonal antibodies, monoclonal antibodies and antibiotics (see Table 1). Recombinant antibodies can be made in unlimited quantities, in stable cell lines, free of virus and associated viral particles. The rAb's can be made entirely of human origin thereby mimicking the body's own natural disease fighting proteins. The rAb's are natural immune-response proteins and therefore are more easily tolerated by the patient. They can also be made as chimaeric molecules, i.e., human/rodent hybrids, thereby being more easily tolerated by the patient than the foreign rodent mAb's. In addition, the rAb's can be characterized and altered for superior characteristics relatively easily. This is accomplished by specifically changing amino acids in the protein. The rAb's are reagents of defined specificity and avidity, i.e., they are highly defined, have reproducible properties and bind tightly to the inducing antigen. Most importantly, in addition to therapeutic use, the rAb's can be used both prophylactically for preventative treatment and <u>in vivo</u> for diagnostic imaging or drug delivery purposes. In some cases the rAb's may be useful as reagents in <u>in vitro</u> diagnostic tests. The delivery of preformed antibacterial rAb's alone or as an adjunct to vaccination and chemotherapy could profoundly improve the management of bacterial diseases.

II.A.4. <u>Technology Background</u>

Antibodies are proteins (figures 1 and 2) produced by cells in the body's immune system (white blood cells, more specifically called B-lymphocytes or B cells) in response to the presence of specific antigens. An antigen

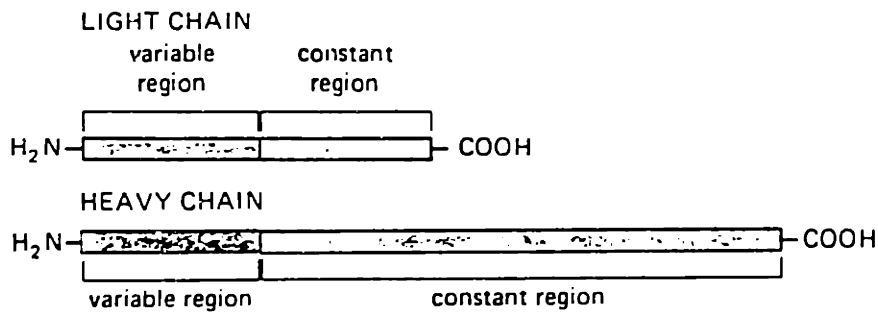
Table 1 Advantages of Recombinant Antibodies

	Property*	Antibodies (rAb) recombinant	(mAb) monoclonal	(pAb) polyclonal
1.	Nature	homogeneous	homogeneous	heterogeneous
2.	Specificity	high	high	low
3.	Variability	low	low	batch to batch
4.	Sensitivity	high	high	variable
5.	Ab Class	one	one	mixture
6.	Affinity	high	high	variable
7.	Reproducibility	high	high	low
8.	Cell Line Stability	high	moderate moderate	none
9.	Species Specificity	human/ chimaera	rodent/ (human)	human/ rodent
10.	Ability to Change Molecule	high	none	none
11.	Ability to Alter Expression Levels	high	none	none

* property definitions:

Nature: a kind or class of Ab distinguished by the characteristic of being identical (homogeneous) or dissimilar (heterogeneous).
Specificity: participating in a reaction with one antigen (bacteria).
Variability: production variablilty, with respect to quantity and quality.
Sensitivity: able to detect very small quantities of the antigen (bacteria).
Ab Class: there exists five different classes of Ab's, each with unique biological characteristics.
Affinity: selective binding characteristics to a particular antigen (bacteria).
Reproducibility: production characteristics.
Cell Line Stability: ability to retain antibody production and secretion.
Species Specificity: biological source of antibodies.
Ability To Change Molecule: ability to manipulate, change the antibody structure.
Ability To Alter Expression Levels: ability to change, increase antibody production in a particular cell.

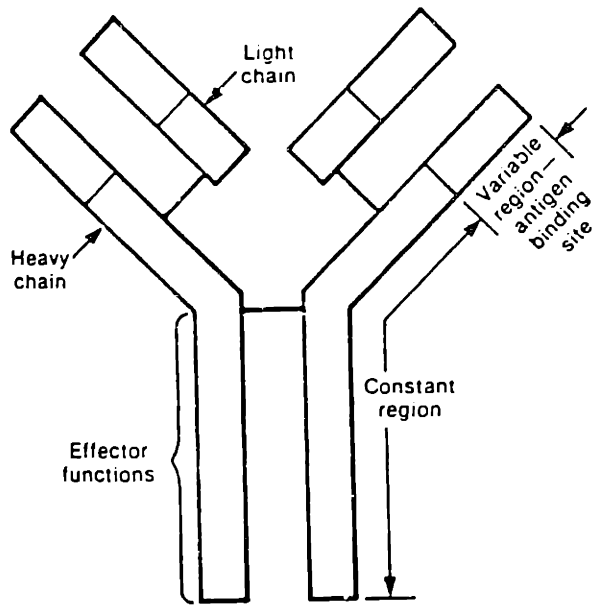
Figure 1 Proteins Comprising the Antibody Molecule



Antibodies are comprised of light and heavy protein chains. The light and heavy chain notation refers to their molecular weights. There exist two classes of light chains (called lambda and kappa), and five classes of heavy chains (called IgM, IgG, IgA, IgD, IgE; the Ig stands for immunoglobulin). Both the light and heavy chains have distinct constant and variable amino acid regions (recall that proteins are "strings" of amino acids). The NH2 refers to the amino end and COOH to the carboxyl end of the molecule, written as such as a matter of convention. For light chains, the carboxyl "constant region" halves of the protein chains of the same class all have the same amino acids (with only occassional differences). The amino "variable region" halves of each light chain, of each class, are all different. For the heavy chains, the amino end variable region is of similar size to that in the light chains (about 110 amino acids). The constant region of the heavy chain is three to four times the size of a light chain (depending on the class).

Source: reference 19

Figure 2 Structure of the Antibody Molecule



An antibody molecule is composed of two identical light chains and two identical heavy chains. A typical antibody molecule may be made up of, for example, two IgG heavy chains and two lambda light chains (from figure 1), and would be called an IgG, lambda antibody. The variable regions of both light and heavy chains comprise the site of antigen binding (attachment). The antigen here may be thought of as the infectious bacteria. Each antibody has two identical variable region-antigen binding sites. The constant regions refer to specific areas of the antibody molecule that are the same from one antibody class to another. In comparison, the variable region is different in each antibody molecule regardless of the class. The effector functions refer to the regions of the antibody molecule within the constant region, that help along the immune response, i.e., elimination of the antigen after the antibody binds to the antigen (see figure 4).

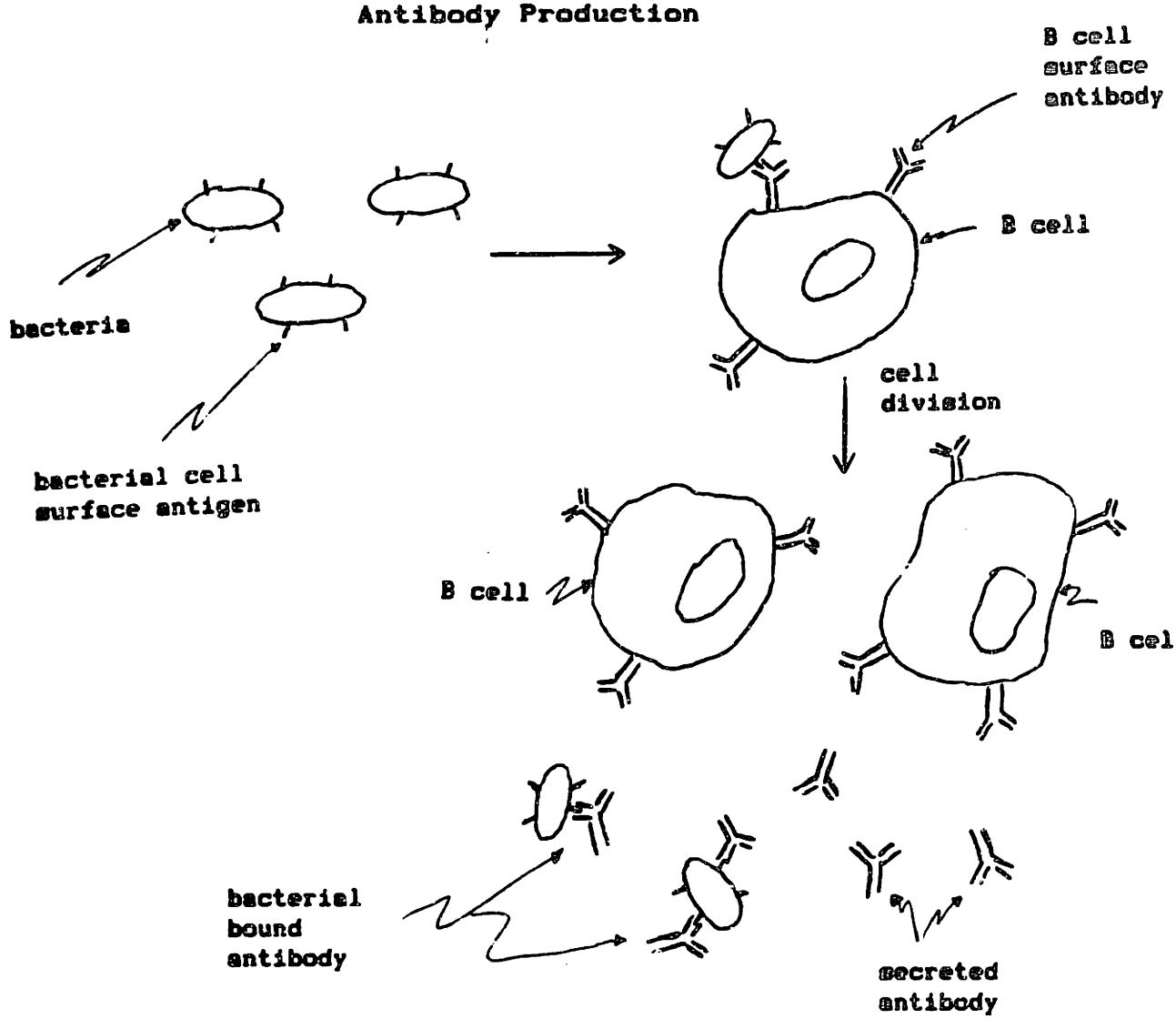
source: references 15, 19.

is any molecule or part of a molecule which appears foreign to the body and activates an immune response, to produce such antibodies (see figure 3) . The antigen, for example, can be a single protein floating in the blood stream or sugar molecule on the cell surface of some blood borne microorganism. Antibodies have exquisite specificity in that they recognize the particular shape of an element on the surface of the antigen. Moreover, they only bind specifically with the antigen that elucidated their production, or with a structurally related antigen. This specificity makes antibodies useful for a number of applications in the diagnosis and treatment of disease.

The mechanism of antibody therapy is that the resulting bacterially induced antibodies bind to the surface of the bacteria (figure 3,4) and cause destruction of the microbes by one of several mechanisms as part of an individuals own, existing immune response. One method is phagocytosis (figure 4), whereby the antibodies coat the surface of the bacteria which facilitates the recognition and ingestion (phagocytosis) of the bacteria by macrophages (a particular type of white blood cell). A second mechanism by which antibodies mediate bacterial killing is through complement lysis (figure 4). This method involves antibody-mediated deposit of complement proteins on the bacterial surface and the formation of holes in the bacterial cell walls/membranes, resulting in cell death. Antibodies adhering to bacteria also prevent bacterial colonization and/or invasion. A third mechanism involves the Ab-coated bacteria activation of a specialized group of cells in the body (K cells) that directly cause bacterial death (figure 4).

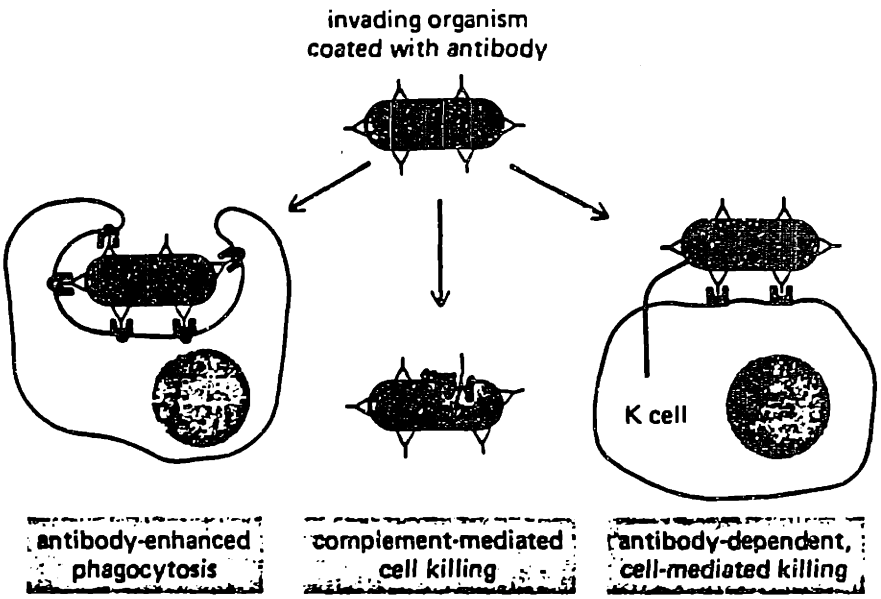
Monoclonal antibody production technology allows the previously impossible task of isolating and growing a single type of antibody producing cell.

Figure 3 Schematic Diagram of Bacterial Induced Antibody Production



The antigen here is the bacteria, or more specifically, some molecule on the surface of the bacteria. The bacteria binds specifically to an antibody on the surface of a B cell in the body. This induces the B cell to divide, expand in numbers and become activated to secrete Ab's that will bind to the inducing bacteria. This can occur in an individuals bloodstream (naturally immunized) or <u>in vitro</u>. (not drawn to scale)

Figure 4 **Schematic diagram of three ways in which Ab's can help eliminate invading organisms**



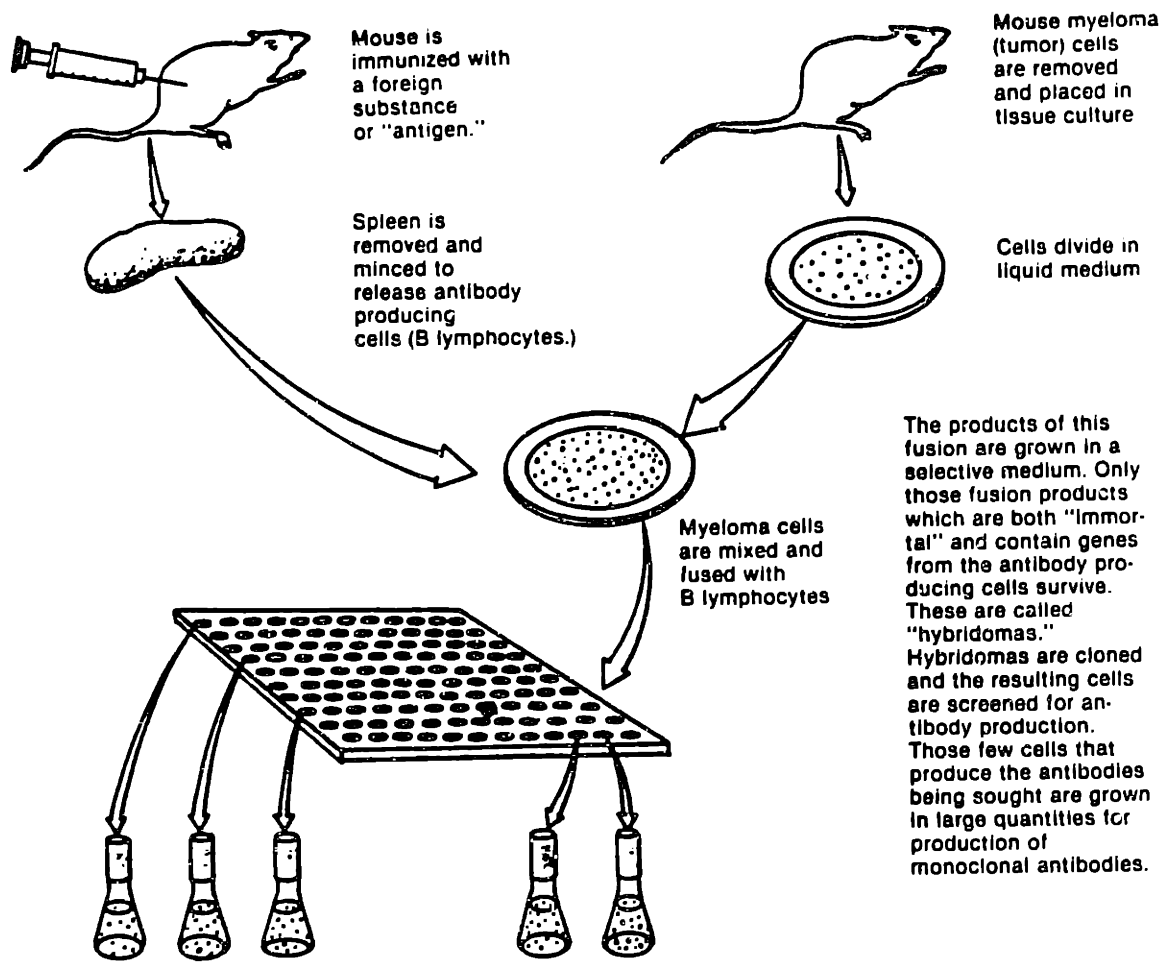
The antibodies from figure 3, bind to the bacteria and then participate in the bacterial elimination from the body. This occurs by one of three mechanisms (see text and reference for a more complete description). The mechanism of elimination is mediated by biological properties located in the constant regions of the heavy chain of the particular antibody.

source: reference 19

Each type of antibody producing cell produces one antibody and is hence monoclonal. Some of the reasons for the importance of mAb's are due to their unlimited supply, defined immunological characteristics, and exquisite specificity for a single antigen (organism).

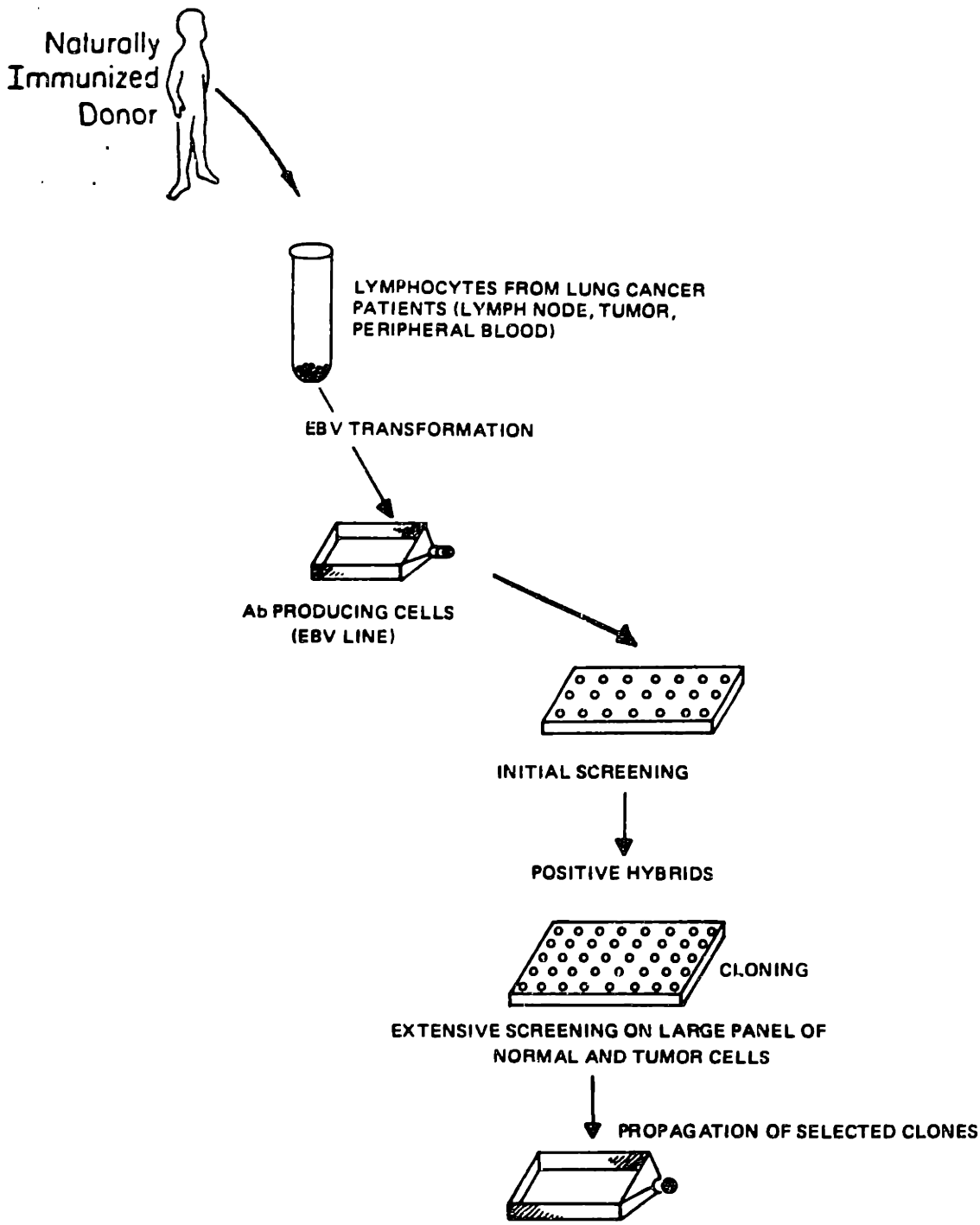
Monoclonal antibody production can be achieved via hybridoma technology (figure 5) or through viral transformation (figure 6). Hybridoma technology involves the collection of spleen cells from rodents (usually mice) which have been immunized with the target antigen (bacteria). Then the fusion of the normal antigen-activated antibody producing cells (a mixture of the mouse's antigen stimulated B cells from its spleen) with an immortal, transformed cell line, usually of similar cell type (mouse myeloma, tumor cell line), is carried out. The result is a "hybridoma" that retains the traits of antibody production and immortality <u>in vitro</u>. The hybridoma can produce the highly specific antibodies and can be maintained indefinitely in culture. The mAb's being produced are chemically and structurally homogeneous. A limiting factor in the application of mAb's to the treatment of human disease, in addition to those listed in Table 1, is the lack of availability of human mAb's in comparison to the abundant mouse or rat derived monoclonals.

Figure 5 Monoclonal Antibody (mAb) Production
Hybridoma Technology



source: reference 15

Figure 6 **Human Antibody Production via Viral Transformation**

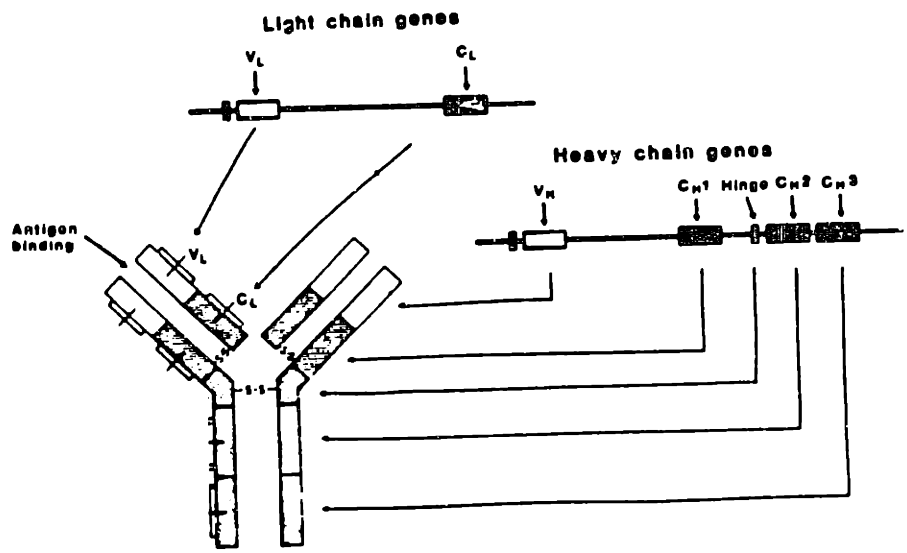


source: reference 20.

There still remains many technological hurdles in the production of human mAb's, especially of pharmaceutical quality. Recently, scientific groups have been able to immortalize normal human Ab producing B cells by viral transformation, primarily using the Epstein-Barr Virus (EBV) (20). Briefly, using this method a normal person's white blood cells (containing the Ab producing cells), naturally immunized, are transformed by the EBV (figure 6). A naturally immunized donor is a normal individual who naturally carries Ab's to the bacteria of interest as a result of some prior exposure. The EBV transformed cells are then selected for the correct Ab producing cell. The EBV transformed cells often produce the EBV virus or associated viral particles. The virus or virus particles can contaminate the "purified" Ab preparation and be injected into a patient. The resulting problem is the potential for the patient to then contract EBV and related disorders. These associated problems create difficulty in getting the Ab therapeutics through the FDA process to licensure. In addition, they would add to liability problems for the producing company. The EBV transformed cells often change their Ab production characteristics within a year's time. In addition, this technique, as with mAb's, does not always produce an Ab with the correct specificity or characteristics. To overcome the limitations in current human Ab production, one can use recombinant DNA technology.

Recombinant antibodies directed against bacterial infections can be produced by cloning and expressing the mAb genes in mammalian cell tissue culture. That is, one first generates either human or rodent mAb's (figures 5 or 6) by one of the above mentioned techniques. The Ab genes are then isolated and cloned (figure 7). Human monoclonal antibodies can be directly expressed in a virus free mammalian cell line. When a rodent mAb is being used used,

Figure 7 Recombinant Antibody (rAB) Production



Specific Ab genes are isolated from the chromosomal DNA in a particular monoclonal antibody producing cell or EBV transformed producing Ab cell (figures 5,6). The V refers to the variable region and the C refers to the constant regions. The L and H subscripts refer to the light and heavy chains respectively. The hinge region is the segment of the protein chain between the first and second constant regions. The S-S regions refer to sulfer chemical linkages in the molecule. Note that the DNA coding regions (the rectangles) of the Ab genes are separated from one another as compared to the alignment in the Ab protein molecule (for a complete understanding of this phenomena of mammalian gene structure please see the source listed below).

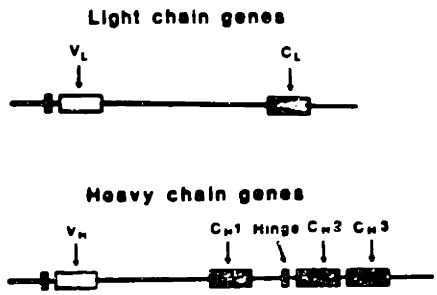
source: reference 21.

one can create a human/rodent chimaeric Ab, leaving only those portions of the rodent Ab intact that are necessary for binding to the bacterial antigen. The remainder of the molecule is made as human in structure as possible, thereby reducing any chance for unnecessary and unwanted immunological reactions against it. This is accomplished by isolating the rodent mAb genes (figure 7), cutting and removing all regions of the gene, but leaving the variable-binding region (figures 1, 2 and 8) intact. The human constant region genes are then joined together to the rodent variable region gene to remake a functional Ab gene. For example, in figure 8, the shaded box regions of the genes could be the human counterpart and the unshaded box regions the rodent counterpart. The chimaeric Ab can then be expressed in tissue culture cell lines as can be done for the human Ab's.

The general principle of genetic engineering in mammalian cells is outlined in figure 9. The foreign gene in this case refers to the human Ab gene containing the information necessary to direct a cell into making an antibody molecule that will bind to an infectious bacteria. This Ab gene (foreign) is joined to a plasmid which has the proper control signals in its DNA (22) to divide and replicate in mammalian cells. The mammalian cell line of choice would be a cell that is the natural host and producer of antibodies (21).

The rAb's can be given more effectively, both prophylactically as well as therapeutically, than other forms of treatment. The prophylactic treatment regimen will represent an entirely new market of patients and use. The rAb's can be used in the absence of or in conjunction with antibiotic therapy. The rDNA technology offers the advantage of manipulating the antibody molecule so as to achieve altered, superior characteristics. The DNA encodes the information to direct a cell to produce a specific

Figure 8 Construction of Recombinant Antibodies



the Ab genes are isolated from the monoclonal cell line

Ab genes joined with expression plasmid

transformation: transfer into mammalian cell line

select for recombinant Ab cells

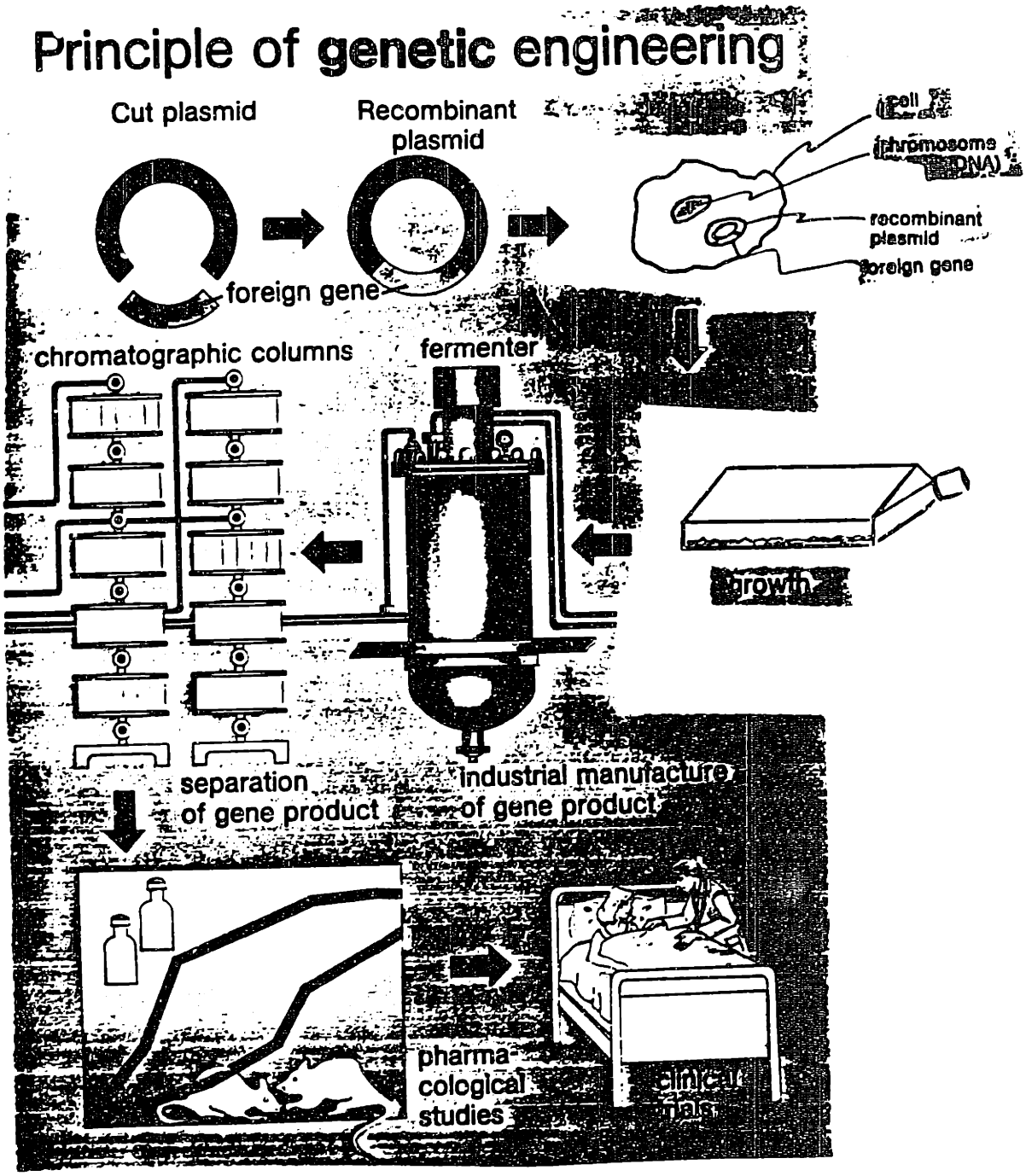
test for presence of rAb

grow in culture

purify rAB's

source: reference 21

Figure 9 Principles of Genetic Engineering

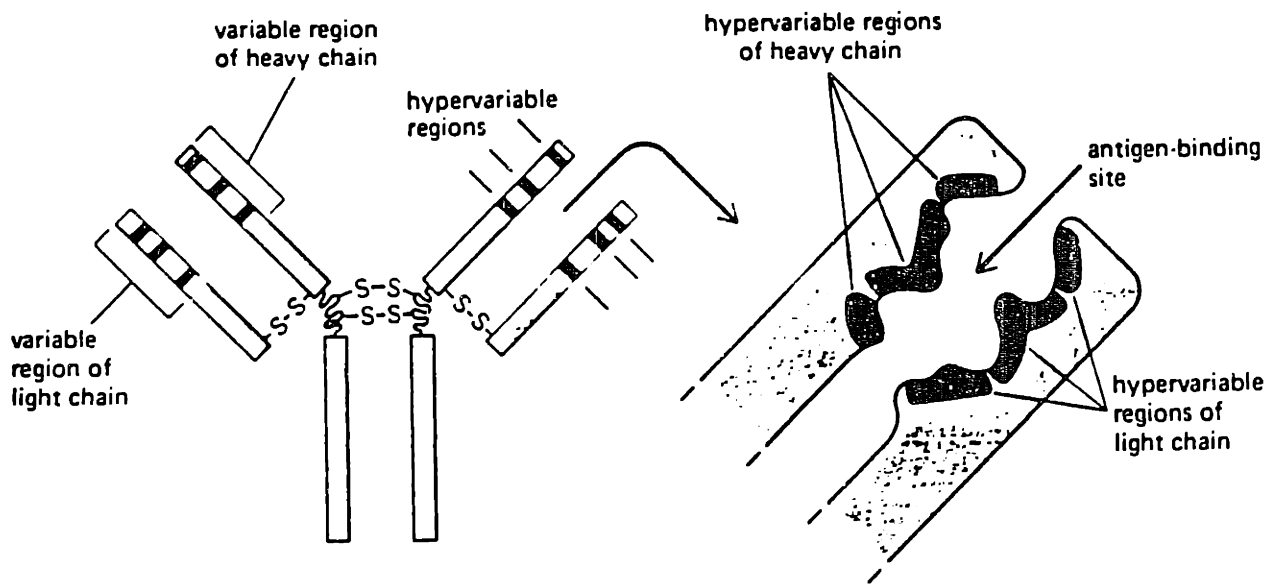


See text for details.

source: reference 15

protein. Briefly, by changing specific sites in the antibody genes (at the DNA level), the resulting amino acid changes in the antibody protein may yield an antibody with better binding characteristics or increased protective efficacy (figures 10 and 11). This is due to the interaction between the particular Ab and the individual's immune response mechanism. For example, the altered Ab may now better facilitate the attachment of the Ab to the bacteria (figure 3) or the macrophages (figure 4) thereby increasing the chance of bacterial elimination.

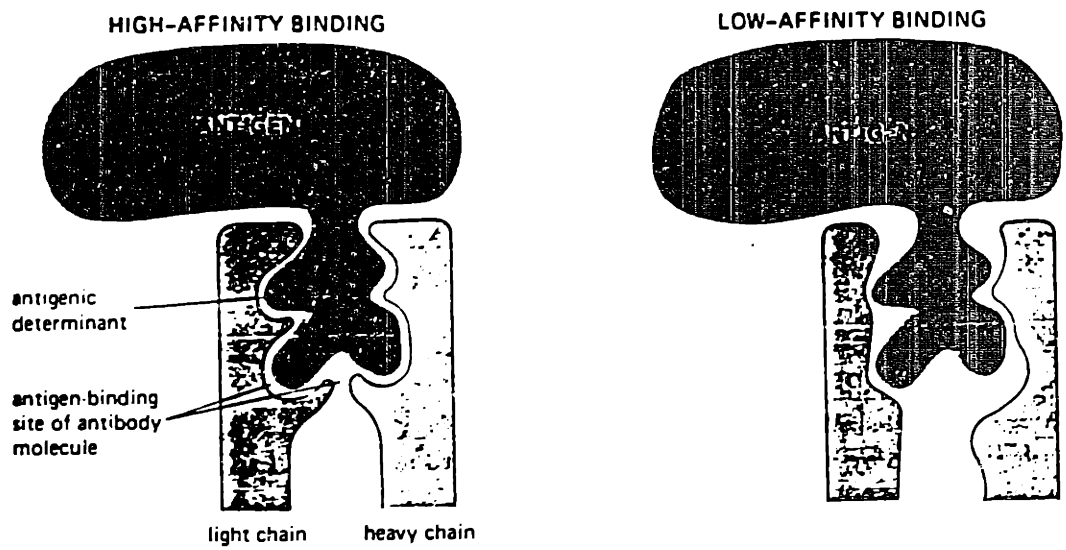
Figure 10 **Schematic Diagram of the Ab-Antigen Binding Site**



The hypervariable regions denote the specific amino acids in the Ab protein, both on the heavy chain and light chain, that actually come in contact with the antigen (infectious bacteria). These amino acids can be changed to alter (increase) the binding of the Ab to the antigen (bacteria).

source: reference 19.

Figure 11 Schematic Diagram of Ab-Antigen Binding Interaction



The antigenic determinant (or bacterial cell surface molecule) is held in the Ab binding site by interactions between it and the Ab amino acids in the hypervariable region. By changing the amino acids in this region one can alter the binding specificity of the Ab to the bacteria (make it a stronger, higher affinity, or weaker binding, lower affinity). Alterations can also be made in the Ab's constant region (figure 2), affecting the mechanism of macrophage binding and bacterial elimination (figure 4).

source: reference 19.

II.A.5. Prospects

Some uses for rAb's and mAb's to bacterial pathogens include:

a) therapeutics

b) prophylactics

c) diagnosis

d) elucidation of a bacterial antigen's role in pathogenicity

e) identification of specific antigens and the grouping, typing and subtyping for epidemiological, taxonomic and evolutionary studies

f) study of the relation of the antigen to transport of materials inside and outside of the bacterial cell and other biochemical functions.

II.A.6. Factors Affecting Business

The path to therapeutic product approval and licensure by the U.S. regulatory authorities is rather long and arduous. The process can take six to ten years to reach licensure of human healthcare therapeutic products. The process is research intensive with major efforts spent on extensive clinical trials and development of commercial technology. The primary goal of the Company is the identification of new, unique drugs that are safe,

effective and broadly patentable. The Company will provide such new drugs (rAb's) to collaborating companies for manufacture and marketing. The Company will receive revenues in the form of contract R&D as early as year two.

When used as <u>in vitro</u> diagnostic reagents the rAb's or mAb's offer the opportunity for recovering some of the R&D costs of the required biotechnologies at an early stage. Currently there are many rapid diagnostic tests on the market that use polyclonal antibodies to detect various antigens produced by bacterial pathogens. However, conventional techniques often produce antibodies that are cross-reactive with other microorganisms. Furthermore, they often have ill-defined specificities. Very large quantities of antibodies are required to detect the bacteria but are often in limited supply. Both mAb's and DNA probe technology will circumvent the diagnostic use associated problems. Both mAb and DNA probe technology are being rapidly developed for use in diagnosis of infectious disease by many companies (see Competition section III C). DNA probe technology refers to the use of specific pieces of bacterial DNA, radioactively or non-radioactively labelled, to be used in diagnosing the presence of bacteria in bodily fluids and other samples (23). The Company will not pursue diagnostic antibodies as a major strategic thrust as it will detract from its focus on therapeutics. It may sell such antibodies if discovered in the course of therapeutic rAb development.

II. B. The Company

The Company will be in the healthcare, therapeutic and prophylactic business. The Company will be organized for the purpose of engaging in the research and development of therapeutic products for the treatment and prophylaxis of infectious diseases. The initial focus is on several major bacterially transmitted infectious diseases. The later focus will be on viral infectious diseases and expansion into other areas using rAb technology (see Potential, section II.C.3.).

Based on scientific observations showing that certain mAb's can be protective against bacterial infections in animal models* (18) as recently as 1984, the Company has devised a product development strategy which it believes distinguishes it from its competitors. Unlike many of its competitors, the Company will focus its efforts on human and human chimaeric rAb's for therapeutics and prophylactics (see Competition). This offers the advantage of generating a drug that will not be rejected as foreign by the body. Moreover, the human rAb's enable prophylactic (preventative) treatment not amenable to antibiotic and many forms of mAb's. Furthermore, rAb's can be easily altered for superior characteristics.

The Company intends to employ such antibodies against bacterial cell surface components. These antibodies will be used in vivo, in conjunction with the patient's immune system, to destroy the invading bacteria

* mAb's have recently been shown to protect animals from bacterial infection by pre-treatment with the mAb prior to experimental infection. In addition, mAb's have been shown to effective in treating animals that already have an infection.

and thereby eliminate the infection. The Company believes that because the specific antibodies are able to discriminate among minute alterations found on the bacterial cell surface, bind to them, and activate the immune response bacterial destruction mechanism, there is significant potential for using them as new commercial products. These new commercial products will be more useful for treatment than all other forms of treatment (as outlined in section II.A.3). In addition, these new products will be better able to detect the presence of specific bacterial diseases. Based on this approach, the Company will continue to develop a host of immunotherapeutic products (rAb's) against a variety of bacterial pathogens.

The primary goal of the Company is to develop rAb's for <u>in vivo</u> use, which must undergo the more governmental regulatory intensive process than <u>in vitro</u> reagents. In the process of such development, the company may discover mAb's that might be useful in diagnosis. Any such diagnostic mAb's will either be sold outright or developed with a joint venture partner.

The ultimate consumer of each rAb developed for therapeutic or prophylactic use will be a patient under a physician's care (see market analysis). The rAb drugs will be sold directly to hospital and independent pharmacies, clinical labs, physicians and research institutions throughout the world.

II.C. The Products and Services

II.C.1. Description

The Company is focusing on the development of two types of product:

1. Therapeutic antibodies for the treatment of infectious disease.
2. Prophylactic antibodies for the prevention of infectious disease.

The production of *in vitro* diagnostic Ab's for detection and monitoring of infectious disease is not a product focus of the Company, per se. The development of mAb's are stepping stones to the Company's major product focus, i.e. rAb's. Should the characterization of the mAb's result in useful diagnosis, they will be sold for a profit or developed in a joint venture. Such a case would be carried out for the purpose of generating income while developing the therapeutic and prophylactic rAb's.

The focus of the company is initially on a few major products in health care. The technology used will be mAb production and rAb production. A list of primary infectious disease product target areas is given in Table 2. These product target diseases are amenable to human Ab prophylaxis and therapy. These bacterial diseases have the following characteristics:

a) there is no current effective vaccine.
b) there is increasing antibiotic resistance.
c) there are significant numbers of new cases each year.
d) there is ineffective present drug therapy.

In addition, the criteria for selecting certain bacteria as product targets for therapy stems from the

Table 2 Infectious Bacterial Pathogens
Product Target Areas

Pseudomonas aeruginosa

Haemophilus influenzae type b

Neisseria meningitidis

Streptococcus pneumoniae

Escherichia coli

Staphylococcus aureus

Salmonella

Klebsiella pneumoniae

Gram negative bacteria

Others

demonstration of antibody-mediated protection (18). Table 3 contains a checklist of some general factors that should be considered in project selection.

Bringing pharmaceutical products to the market as fast as possible and generating positive cash flows, while at the same time pursuing long term and costly development in joint ventures with larger firms, is a key to the Company's strategy. The development of therapeutic and prophylactic Ab's will be in a manner that reduces direct costs and limits financial risks. The Company will focus on collaborations and licensing of the mAb's from academic labs for it's first two products. Since the first step in rAb production is to obtain mAb's, the Company will be able to speed up the product development by initially licensing the first two monoclonal antibodies from academic labs that have previously developed them.

The Company will enter into contracts with established companies who will manufacture and market the Company's products. The relations with outside institutions, other companies and universities, will form an important part of the Company's business strategy. The Company will expect to both receive and pay out royalties as a result of its operations.

Initially, the Company does not plan on becoming an independent pharmaceutical company. It will work through the licensing and joint ventures with established firms. The Company may be seen as a form of service company as it will be supplying the key components of a form health care (rAb's to infectious bacteria) to other companies. In this sense the Company may be able to obtain high royalties (10-20%) on their technology licenses.* The Company policy of commercializing research results performed outside the Company speeds up the process of new product introduction. An additional element of the Company's strategy will be to issue non-exclusive licenses to marketing partners in order to cover the world market.

Table 3 **Factors Influencing Project Selection**

SCIENTIFIC FACTORS	MARKETING CONSIDERATIONS	ORGANIZATIONAL AND OTHER ELEMENTS
Interrelationship with other research activities—synergistic advantages or competition with other programs.	Projected sales and profits from effort.	Relationship to activities at other research centers or units within the company.
Probability of achieving project objectives.	Relationship to need as reflected by current state of consumer satisfaction.	Timing of project with respect to other activities in marketing, research, etc.
Time required to achieve project objective.	Status and efficacy of current competitive products or means of meeting consumer need.	Manufacturing capabilities and needs.
Impact on balance of short- and long-term programs within research.	Compatibility with current marketing capabilities and strengths.	Prestige and image value to the company.
Estimated cost of the project in the coming year and to completion.	Influence of new competitive products under development.	Effect on organizational esprit de corps and attitudes.
Utilization of existing research talent and resources.		Impact of governmental and public opinion and other environmental pressures.
Value as a means of generating experience and gaining a technical expertise in a field—a foundation for future research activities.		Alternative uses of scientific personnel and facilities if project dropped after a few years.
Need for critical mass of expertise and activity to ensure progress.		Moral compulsion to develop drugs meeting medical need but having little or no profit potential.
Elasticity of resource input and probable output relationships.		
Patentability or exclusivity of discoveries from project.		
Competitive research effort in the area—in academic and government research centers.		

Source: reference 24

II.C.2. Proprietary Position, Patents

While the exact role of patents in the biotechnology industry is far from clear at present, patent protection is expected to play a key role in ensuring that companies gain adequate returns on their massive R&D expenditures involved in discovery, development and commercialization of new therapeutic drugs. In the pharmaceutical industry patenting has traditionally been important (25). In 1986 the Reagan administration unveiled a policy designed to pressure trading partners into protecting U.S. patents, trade-marks and copyrights.

The basic mechanisms of mAb production are patent free due to the lack of patent application by the co-discoverers. Current patent situation in the rAb area is unclear. Some of the Ab expression technology may have to be licensed, but may only apply to chimaeric antibodies (i.e., human/mouse hybrids). The development of a bacterial specific antibody can itself be patented, as well as the composition of matter and its use. Any alterations made to the molecules may offer additional patent protection. The development of efficient mammalian cell expression systems can also be patented. In any case, a thorough review of the patent literature will be necessary. Some key company and university patents to be examined will include Genentech, Inc. (S.S.F., CA), The City of Hope (Pasadena, CA), Stanford University (Palo Alto, CA), and Columbia University (N.Y., N.Y.), where much of the inital work of rAb's has been carried out.

* Centocor, Inc. (Malvern,PA), A company developing mAb's for cancer diagnosis and therapy, has adopted this strategy and is obtaining such high royalties.

II.C.3. Potential

The Company's competitive advantage lies in the in-house expertise and in its products:

- treatment for specific classes of infected patients
- these reagents are non-existing in market today
- circumvents bacterial antibiotic resistance
- uses body's own natural immune response mechanisms
- reagents are non-toxic, highly bacterial-strain specific
- reagents are non-immunogenic (human rAb's)
- reagents can be used prophylactically
- can be produced in an unlimited supply

The expansion of the product line will be into all the known severely life-threatening pathogenic bacteria (10). Additionally, the company may develop rAb's for other pathogenic microorganisms (viruses).

The development of rAb technology offers the tremendous advantage of an enormous future development of related antibody products with a completely different end use. A partial list includes:

a) immunotoxins, vectorially delivered drugs or toxins to specifically kill cancer cells (26);
b) targeted immune responses: to kill cancer cells, inhibit autoimmune disease (27);
c) cancer treatment (28,29);
d) transplantation, inhibition of allograft rejection (30,31);
e) rAb's to drugs, used to reverse the adverse effects of a wide variety of biologically active molecules (32);
f) in vivo imaging (33);
g) therapeutic drug monitoring (34);
h) lymphokine targeted immune responses/delivery;
i) drug receptor agonists/antagonists ;
j) use of rAb in industrial purification.

II. D. Entry and Growth Strategy:

During the last ten years there has been a proliferation of over 100 new biotechnology companies (15). Due to proprietary information and technological gaps between existing companies and potential new entrants, there has been a decrease in new start-ups since 1984. The primary entry barriers in the biotechnology industry are (i) the cost of R&D, governmental regulation, (ii) access to distribution channels (iii) technological uncertainty and (iv) proprietary technology and patents.

II.D.1. Costs of R&D, Governmental Regulation

The costs of entry into the biotechnology industry are related to expenses involved in R&D. The R&D costs are closely tied to the costs of governmental regulation. In the U.S., the National Institute of Health (NIH), the Food and Drug Administration (FDA), the Environmental Protection Agency (EPA), the U.S. Department of Agriculture (USDA) and several executive agencies all have authority over which they can regulate biotechnology research and development (35). The most highly regulated areas are human pharmaceutical drugs and *in vivo* diagnostics agents. The greater than $50 million required to finance the large clinical trials and long trial periods can be prohibitive to many new firms. However, large profitability awaits those who successfully make this step. It has already been the case that under special circumstances, i.e., dire need, as with human growth hormone (Genentech, Inc.), the FDA can speed up this process and therefore reduce the time and cost. Furthermore, there are plans in the U.S. government to speed up the approval of drugs for serious ailments, which would reduce the costs.

The long range growth strategy of the Company, is to develop infectious disease pharmaceuticals that will be used to treat life threatening situations, where current therapy is ineffective. Therefore, the Company's products may fall under special FDA considerations. This would lead to a decreased time to licensing than otherwise. Additionally, the inital product focus will be on antibodies for infectious disease where animal models and pharmacology studies are already in place. Therefore, the Company will not have to develop them.

Considerably less expensive than pharmaceuticals are the costs of supplying monoclonal antibodies to manufacturers in in vitro diagnostic kits. For example, in vitro diagnostics do not require the sterilization process and formulations necessary for the final product, as is required for other in vivo diagnostics or pharmaceuticals. The costs are estimated to be about $4M over a three year period in U.S. However, development of the final kit by the manufacturer may cost an additional $10-20 million. The Company will provide any mAb's it develops as reagents to a manufacturer for further diagnostic kit development.

II.D.2 Access to Distribution Channels

A major entry barrier exists to new companies not manufacturing and distributing their own products. The selection of appropriate channels of distribution is crucial to ensuring a marketing success. Tapping into existing distribution channels within large established companies can, however, relieve this entry barrier. The Company's strategy will be to enter into a joint venture with an established firm in the infectious disease area (see marketing strategy).

A major coup for the pharmaceutical industry came through governmental lobbying by the new biotechnology firms and large pharmaceutical companies. The Senate recently approved legislation permitting the export of drugs that have not yet won approval for sale in the U.S. (36). This has strategic implications in stopping the erosion of the U.S. innovations and transfering of our technologies. It further increases the chance of profitability by marketing the Company's drugs in other countries, by other companies, before U.S. approval.

II.D.3. Technological Uncertainty

Technological strategies in the biotechnology industry are constrained by the technological uncertainties inherent in this industry. The increased factor of risk, raises the opportunity cost of capital for a company. As such, established companies affected by the new technology have an initial reluctance to invest. The technological uncertainties in biotechnology have also impeded established companies decisions to jump off the "S curve" from an existing technology onto a new "S curve", a new technology (37) (an S curve is a graph of the relationship between the amount of effort put into a project and the productivity or results one gets out). This can be seen by the established pharmaceutical companies which did not invest in biotechnology until after 1980, when many small firms were already beginning commercializing the "new" biotechnologies as early as 1972.

Competing technological processes and uncertainty over which products to choose for a new biotechnology market further add to the risk factor. In the cancer field, there are several new products and technologies simultaneously under development. In almost all these cases the clinical data is incomplete and companies cannot devote equal resources to all these products. This factor is still showing signs of impeding large companies from entering this field. The in-house expertise and single technology (rAb) focus that can be applied to many different diseases and industrial applications, offer the Company a distinct advantage over the larger competitors.

II.D.5. Common Strategy Elements Adopted by Biotechnology Companies

New biotechnology companies must develop a defensible competitive position whether they are in products or services. The common elements in their strategies include: the methods of financing, the strategic alliances with established corporations and forward integration into mature independent companies.

The pattern of financing that has been followed by most new firms is funding their early development by venture capital, with one to three rounds of financing, and contract R&D. A few years down the road they have initial public share offerings in the hopes of raising large amounts of cash, followed later by public share offerings. Once approaching clinical trials and further development, the new firms finance their expansion through R&D limited partnerships. Most, if not all, new biotechnology firms run at a deficit for the first few years due to the enormous R&D expenses and investment in plant.

Many new companies evolve through various forms of strategic alliances with established firms, distribution by other companies of products manufactured in-house and, finally (hopefully), their own manufacturing. The forward integration into a fully integrated pharmaceutical company (self manufacturing and marketing) is a very large step for all the new biotechnology firms. It is the likely step in which many will be unable to make successfully.

II.D.6 Focused Products Strategy of the Company

The Company will adopt a focused products strategy. In a new firm where resources are limited, all the resources are used to focus on a narrow market. This maximization of resources includes the use of research personnel, the optimum amount of contract R&D versus in-house development and development of manufacturing and marketing groups. Since the Company has clearly targeted its goals, it can focus its arrangements with other companies to fit its strategic goals rather than forming opportunistic arrangements depending on what R&D program comes along. The strong internal organization and clear market focus of the Company will allow it to capitalize on its technological advantage over the larger pharmaceutical competitors. The Company can compete on the basis of having new products and the most technologically advanced products on the market.

The focused products strategy has been adopted by those companies that have identified a specific market niche. The Company, with its product/technology focus, will hope to obtain an overall product differentiation or overall cost leadership.

Technological leadership is the major strategy that must be undertaken by the Company. The Company must engage in pioneering activity as it does not yet have any product sales. As a result it will not have the choice between technological leadership and followership as do the larger, established companies.

Due to the absence of patents in the 1970's the biotechnology methodology is widely diffused. All the firms worldwide have access to the technology. As a result, the uniqueness of a firms skills, in large part, is not as relevant in biotechnology as it was in the electronics industry. It is the applications of the

technology which determines which strategies to undergo.

For all biotechnology products, getting the innovative product to the market first may mean the ability to satisfy a large demand and achieve a dominant market share while competitors are still at the development stage. The first to the market is an important strategic goal to meet as it gives the leader the reputation and advantages over competitors in terms of customer behavior (38). In the pharmaceutical market it is not unheard of for a company to abandon the development of a new drug when it has been beaten in the race to be first to the market (39). The Company's goal will be to have its first therapeutic rAb on the market by year seven, from the Company's inception.

The major factors affecting technology strategy in the Company are:

a) the technology/opportunity applications unique to the Company,
b) leadership factors concerning key personnel,
c) first to the market opportunity/advantage,
d) adaptability of technology processes and equipment to differentiate products,
e) leadership factors concerning regulatory approval,
f) leadership factors concerning patent position.

III. Market Research and Analysis

III.A. Customers

While the patient is the ultimate consumer of the pharmaceuticals, the law requires that at least one intermediary stand between the manufacturer and the consumer, i.e., the physician. It is illegal for the pharmaceutical manufacturer to sell prescription drugs directly to the patient. The market for pharmaceuticals is unique in the importance of the influence of a non-purchaser (the physician) on the purchasing habits of the ultimate consumer (the patient). The role of the physician is that of a decision maker.

The products incorporating rAb for therapeutics and prophylactics may be expected to be developed for a variety of health care commercial markets. The physical distribution of the Company's pharmaceuticals will be carried out through pharmacies.

The markets for the therapeutic and prophylactic rAb's will include:

a) community hospital pharmacies b) government hospital pharmacies (federal, state, local)	primary
c) independent pharmacies d) physicians e) research laboratories (universities) f) veterinary market	secondary

The therapeutic/prophylactic drugs will be largely dependent on quality and uniqueness. In some cases, where there is a therapeutic choice for a particular infectious disease, there will be some slight price dependency.

The need for new products to combat infectious disease, i.e., the Company's proposed products, has been expressed by physicians, hospitals and other health care practitioners as evidenced by the many reports in the literature (1-14,40).

III.B. Market Size and Trends

The U.S. market size for the company's products, rAb's to bacterial infectious agents, has been estimated from statistical data compiled by the Center for Disease Control (CDC), U.S. Department of Health and Human Services, and from various literature references (see tables). The European market studies for this business plan includes the United Kingdom (U.K.), France and West Germany and has been compiled from various documents from those countries (see sources in tables).

In the case of therapeutic treatment, the data represents the number of cases per year of particular bacterial infections reported, with extrapolations made to entire populations. For prophylactic treatment, estimates were made from the potential use of therapy in situations where the particular bacterial agents have a high probability of occurring, as indicated in the various literature sources (1-14).

In general, all the numbers reported are conservative, as they represent extrapolations of numbers reported from hospital surveys, which are not monitored with a high degree of accuracy. In addition, many diseases do not get properly documented, or documented at all, and therefore never reach the CDC's or other reports.

If we look at the size of the entire anti-infective drug market, we see that it is quite large, approximately $4.9 billion in 1983 (Table 4). The anti-infective market

Table 4

Manufacturers U.S. and Foreign Sales of Anti-Infective Drugs for Human Use

	$$$$$$ Millions		
	1981	1982	1983
All Pharmaceuticals:			
U.S.	12,110	14,156	16,219
Foreign	9,895	9,902	9,645
Total U.S. and Foreign	22,005	24,058	25,864
Anti-Infective Agents:			
U.S.	2,034	2,406	2,822
Foreign	2,305	2,208	2,054
Total U.S. and Foreign	4,339	4,614	4,876

Source : reference 41.

is growing at about 5-6%/year. The estimate for 1987 is approximately $6.0 billion.

The Company's initial products will include drugs for the following bacterial infections:

Pseudomonas aeruginosa
Haemophilus influenzae type B
Neisseria meningitidis
Streptococcus pneumoniae
Escherichia coli
Klebsiella
Salmonella

Table 5 shows the numbers of nosocomial infections in the U.S. and Europe (as defined above). Nosocomial refers to hospital-acquired infections. In other words, those infections incurred while already in the hospital for some other reason.

Of the major nosocomial bacterial agents, Pseudomonas, Escherichia coli and Klebsiella are three of the Company's initial product targets.

Pseudomonas represents the largest potential market for anti-bacterial drugs due to its present and increasing role as opportunistic pathogen (43), i.e., a ubiquitous organism that takes advantage of the immunocompromised host. Its prevalence in hospital settings and in immunocompromised patients is alarming (44). The total number of cases per year of Pseudomonas needing therapeutic treatment is estimated to be over 1.6 million, which includes the U.S. nosocomial and European nosocomial markets (Table 5). The European community acquired market would serve to further increase the number of treatable cases per year significantly. For prophylactic treatment the total number of incidence of use per year is estimated

Table 5

Nosocomial Infections in the U.S.(1) : Major Bacterial Agents
(numbers in 1000's)

Infectious Agent	total isolates reported (2)	total estimated isolates in the U.S. (3)	total estimated isolates in Europe (4)	U.S. and Europe totals
Escherichia coli	5.3	723	1,787	2,510
Pseudomonas aeruginosa	3.4	462	1,142	1,604
Enterococci	3.1	420	1,039	1,459
Staphylococcus aureus	3.1	420	1,038	1,458
Klebsiella pneumoniae	2.2	301	744	1,045
Staphylococcus coagulase	1.9	257	634	890
Enterobacter spp.	1.8	240	593	833
Candida spp.	1.6	222	550	772
Proteus	1.5	209	516	725
Serratia spp.	.7	95	234	329
other fungi	.5	49	168	217
Group B Streptococci	.4	48	118	166
all others	3.3	453	1119	1,572

Footnote

(1) reference 42.

(2) total isolates reported: represents reports surveyed from 51 U.S. hospitals (29,562 total cases reported out of 51 hospitals).

(3) total estimated isolates: extrapolated from total isolates reported, taking into account total U.S. Hospitals (1986) = 7,000.

(4) Europe here includes only the U.K. (4500 hospitals), W. Germany (7000 hospitals), and France (5800 hospitals). Sources include: Daten Des Gesundheitswesens (1984 edition) Statistisches Jahrbuch (1983) Sante Securite Sociale: Statistiques et Commentaries (No. 1, 1984) OPCS Monitor DH2 (84/4) Annual Abstract of Statistics (1984) Services Statistics for Northern Ireland (1983)

to be approximately 11.6 million, in the U.S. alone (Table 6). Adding in an estimate for the number of community acquired and non-reported Pseudomonas cases, the therapeutic treatment market comes to approximately $1.9 million (1,141,800 + 763,900, Table 6).

Other major nosocomial bacterial infections the Company's products will address are Escherichia coli, over 2.5 million cases per year, Staphylococcus aureus, approximately 1.5 million and, Klebsiella, approximately 0.8 million, all for therapeutic treatment (Table 7).

Table 7 shows an estimated 800,000 cases per year of Salmonella infections requiring treatment in the U.S. alone. Studies have estimated that the actual number of Salmonella cases per year in the U.S. may be as high as 4,000,000 (46) while only about 40% of these cases require anti-microbial treatment, this would bring the therapeutic market up to 1,600,000.

Additional Company products will target infectious agents responsible for bacterial meningitis (Table 8). The therapeutic markets for Haemophilus influenzae type b, Neisseria meningitidis and Streptococcus pneumoniae as causitive agents in meningitis are, respectively, over 1.9 million, 0.73 million and 0.40 million. The prophylactic market for these agents are 1.1 million, 0.38 million and 0.17 million, respectively. Community acquired bacterial pneumonia contributes a significant cause of morbidity and mortality in the U.S. (47). Table 9 shows additional therapeutic markets for Streptococcus pneumoniae, Haemophilus influenzae type b and Pseudomonas aeruginosa, in cases of community acquired bacterial pneumonia.

The total dollar amount for each of the aforementioned products is listed in Table 10. The therapeutic markets for each drug are in the $85,000,000 to over $400,000,000 range. The prophylactic markets for each drug are also in this category. The numbers shown in table 10 are derived

Table 6 Pseudomonas aeruginosa Market U.S. (1)

assume use in:	total cases/yr	percent potential infected	total cases potential infected
operations of musculoskeletal system (2)	5,031,000	4%	201,900
skin grafts	157,000	12	18,800
cardiac catheterization	681,000	2	13,600
open heart surgery (3)	602,000	2	12,000
trauma patients (4)	3,580,000	12	430,000
haematopoietic system disorders	397,000	4	16,000
cystic fibrosis	100,000	30	30,000
gastrointestinal major surgery (5)	1,040,000	4	41,600
total	11,588,000		763,900

prophylactic U.S. market: 11,588,000 cases/yr

estimated therapeutic U.S. market: 763,900 cases/yr

Actual therapeutic market:
Nosocomial (U.S.) market : 462,000 cases/yr

Nosocomial (European) market: 1,141,800 cases/yr

total nosocomial therapeutic market U.S. & Europe 1,603,800 cases/yr

1. references 45, 10, 42, 43.
2. includes: fractures, disc, spinal column, cartilage, knee, hip replacement surgery.
3. includes: pacemaker insertion and repair.
4. includes: injury, poisoning, lacerations and burns.
5. includes: partial gastrectomy, resection intestines and appendectomy.

Table 7

Other Bacterial Infections Nosocomial Market
(no. cases/yr)

(U.S., U.K., France, W. Germany)

Escherichia coli (1)	Staphylococcus aureus (1)	Klebsiella (1)
2,510,000	1,457,000	774,000

Salmonella (2)
800,000

1. Data obtained from Table 4.

2. reference 46. An estimated 2,000,000 cases of Salmonella occur each year in the U.S. alone, 40% of these cases require anti-microbial treatment. Data for Salmonella represent the U.S. market only.

Table 8

Bacterial Meningitis (no. cases/yr)

Infectious Agents (1)
(numbers in 1000's)

	Haemophilus influenzae type b	Neisseria meningitidis	Streptococcus pneumoniae
U.S.:			
age <5 yrs	10.7	1.8	1.3
>5 yrs, adults	300.0	103.5	34.5
Total U.S.	310.7	105.3	35.8
U.K.	266.4	91.4	39.7
W. Germany	600.0	392.4	288.0
France	741.5	253.0	110.0
Total	1,607.9	736.8	437.7
All Total Therapeutic Market	1,918.6	742.1	473.5
Prophylactic Market U.S. & Europe (use in respiratory operations)	1,131.0	388.0	169.0

1. assume: Haemophilus influenzae type b, 67% ; Neisseria meningitidis 23% ; Streptococcus pneumoniae 10% of bacterial meningitis cases U.K. pop 56,010,000; France 53,713,000; W.G. pop 61,566,000.
2. reference 47, see Table 6.

Table 9

Additional Markets (U.S.)
Community Acquired Bacterial Pathogens

Bacterial Agent	Percent of cases/yr	Number of cases/yr
Streptococcus pneumoniae *	36%	276,000
Enteric gram neg. bacteria	16	123,000
Haemophilus influenzae b *	15	115,000
Legionella pneumophilia	14	107,000
Staphylococcus aureus	8	61,000
Pseudomonas aeruginosa *	3	23,000
Serratia marcescens	2	15,000
Acinetobacter	1	8,000
Anaerobes/other bacteria	4	30,000
	total number of cases =	768,000

Source: reference 10.

Asterisks represent additional markets for the Company.

Table 10

Selected Bacterial Infectious Disease Markets ($) (1)

(U.S., U.K., France, W. Germany)
(numbers in 1000's)

	therapeutic(2)	prophylactic(2)	total
Pseudomonas aeruginosa	$ 192,870	$ 229,760	$ 422,630
Haemophilus influenzae b	203,360	22,620	225,980
Neisseria meningitidis	74,210	7,760	81,970
Streptococcus pneumoniae	74,950	3,380	78,330
Escherichia coli	178,700	?	178,700
Klebsiella	63,370	?	63,370
Salmonella	80,000		80,000
total market value/year	$ 867,460	$ 263,520	$ 1,130,980
		approximately	$ 1.13 billion

1. Data taken from Tables 4-9.
2. Price based on $100 per therapeutic treatment and on a $20 per prophylactic treatment.

by estimating that each therapeutic treatment will cost approximately $100 per patient and that each prophylactic treatment will cost approximately $20 per patient. These numbers reflect a single dose therapeutic treatment and a single dose prophylactic treatment.

It should be noted again that it is felt that the numbers shown in Table 10 represent conservative estimates of the total markets due to a) innaccurate case reporting, b) lack of incidence reporting, c) data from other countries, not shown here. There is no formal surveillance system in any country to estimate accurately the true number of cases of infectious disease that occur each year. Additionally, the costs per treatment are also conservative estimates. Typical antibiotic treatment ranges from $15-400 per day per patient, and can be higher (48). Therefore the cost as estimated above could be significantly higher, by as much as 400%.

III.C. Competition

The basic technology of mAb production and genetic engineering (recombinant DNA technology) is widely diffused worldwide. This includes both the academic and industrial laboratories, including the major pharmaceutical companies. While there have been more than a dozen new companies formed to produce mAb's, it is not apparent which companies, if any, are focusing on rAb's as a therapeutic modality. Furthermore, the majority of potential competing companies are addressing cancer diagnostics and therapeutics. However, the area of mAb based technology is intense and expected to increase in the future as a numberof large, established companies diversify into the field.

The Company feels that the threat of the competition in the prophylactic and therapeutic areas is small to moderate due to the competitors' lack of focus and/or lack of in-house expertise in recombinant DNA technology.* However, large established companies have the possibility of entering into the market later with a late-entry followership or late-entry leadership strategy (38), due in part to their large financial resources. The competition in the infectious disease diagnostics market is definitely more intense.

The large pharmaceutical companies like Bristol Myers/Genetic Systems, Bayer/Molecular Therapeutics, Johnson & Johnson and Becton Dickinson may pose a threat due to their greater financial, production, and marketing capabilities. Bristol Myers/Genetic Systems are developing mAb's for infectious disease diagnosis, using either murine or human (EBV derived) mAb's. Bayer/Molecular Therapeutics are developing human mAb's for Pseudomonas aeruginosa infections, and not pursuing other infectious diseases. Johnson and Johnson, Becton Dickinson, Eli Lilly, Dupont/New England Nuclear, Hoffman La-Roche, and Abbott Labs are all involved with mAb based diagnostics but their primary focus is on cancer. Their involvment, if any, with infectious disease is unknown at this time. Eli Lilly may represent the biggest potential competitor in respect to the large pharmaceutical companies. This is due in large part to their in-house expertise in recombinant DNA technology development and acquisition of Hybritech, Inc.,

* recombinant DNA technology is a skilled art, which takes "talented hands" to make it happen, even in the face of the numerous textbooks outlining the specific protocols (professional opinion).

a small biotechnology firm focusing on mAb production and diagnostics.

The smaller sized competitors (relative to the established pharmaceutical companies) include Centocor, Xoma, Cetus, Monoclonal Antibodies, Inc. and Integrated Genetics. All these companies have established strong R&D groups in the area of monoclonal antibody production and are seeking to develop monoclonal antibody based products. These companies are focusing primarily on mAb diagnostics. Where they are applying these monoclonal antibodies as therapeutics to bacterial diseases, they are focusing on inhibiting the secreted toxins and not the direct destruction of the bacterium. All these companies are focusing on human monoclonal antibodies, not recombinant antibodies. Centocor is now building up their R&D into recombinant Ab's, but their primary focus is on cancer. Cetus may represent the primary competitor, with strong rDNA technology but they lack focus in this area. Cetus' focus is on cancer diagnosis and therapeutics. Integrated Genetics is using DNA probe technology for infectious disease diagnosis, specifically Salmonella, Campylobacter and Shigella (gastro-intestional diseases).

The Company feels that its ability to compete will be based on the successful development of new products altogether, new applications of competing products, enhanced characteristics of competing products or more efficient production mechanisms.

The production of such products is dependent on maintaining both scientific and technical superiority, the protection of proprietary information and processes. In addition, the production of the Company's products will depend on the successful commercialization of the technological developments, success in joint ventures for manufacturing and marketing and relative ease with which the Company or joint venture partner can obtain

governmental regulatory approval and licensure.

The Company feels its ability to produce and express recombinant antibodies to be the most critical factor in successfully competing in the production of human antibodies for both therapeutic and prophylactic use.

III.D. Estimated Market Share and Sales

The main feature of the Company's drugs that will make them marketable in the face of current and potential antibiotic competition is the ability of the Company to treat diseases for which the current therapy is ineffective, or does not exist. The prophylactic use also represents a new type of therapy approach, as it obviates the need for antibiotic therapy and production of resistant bacterial strains.

Tables 11a-e represents the estimate market share and sales of each of the Company's products for the first six years after FDA approval of its drugs (years 7-12). The data is broken out into therapeutic and prophylactic markets: total estimated markets in units and dollars; estimated market share for the Company in percent, units and dollars. A total estimated therapeutic and prophylactic Company market share for each infectious disease product, in dollars, is calculated. The estimated Company share of the prophylactic market for Streptococcus was negligible and was not calculated. The assumption of 5% per year inflation was included into the therapeutic and porphylactic costs. A market growth of 5% per year was included. One unit = one patient dose.

The data in Table 11 assumes that the Company's first product will be on the market in year seven from the Company's inception. It estimates sales revenues from market data represented in section III B, Table 10, and

Table 11a

Estimated Market Share

Pseudomonas aeruginosa

	Year					
	7	8	9	10	11	12
	(numbers in millions)					
Therapeutic Market						
1. estimated total market (units)	2.71	2.85	2.99	3.14	3.30	3.46
2. estimated total market ($)	387.00	421.00	464.00	512.00	564.00	622.00
3. estimated market share (%)	4.00	8.00	20.00	40.00	50.00	60.00
4. estimated market share (units)	0.11	0.23	0.60	1.26	1.65	2.08
5. estimated therapeutic market share ($)	15.47	33.69	92.83	204.72	282.00	373.00
Prophylactic Market						
6. estimated total market (units)	16.17	16.97	17.82	18.71	19.65	20.63
7. estimated total market ($)	455.00	501.00	553.00	610.00	672.00	741.00
8. estimated market share (%)	0.10	0.20	0.50	1.00	5.00	10.00
9. estimated market share (units)	0.02	0.03	0.09	0.19	0.98	2.06
10. estimated prophylactic market share ($)	0.45	1.00	2.76	6.10	33.60	74.10
11. total estimated market share ($)	16.00	35.00	96.00	24.00	31.00	447.00

Table 11b **Estimated Market Share**

Haemophilus influenzae type b

	Year					
	7	8	9	10	11	12
	(numbers in millions)					
Therapeutic Market						
1. estimated total market (units)	2.90	3.00	3.20	3.30	3.50	3.70
2. estimated total market ($)	402.00	443.00	488.00	540.00	593.00	657.00
3. estimated market share (%)	4.00	8.00	20.00	40.00	50.00	60.00
4. estimated market share (units)	0.12	0.24	0.63	1.32	1.73	2.19
5. estimated therapeutic market share ($)	17.00	36.00	98.00	215.00	296.00	394.00
Prophylactic Market						
6. estimated total market (units)	1.60	1.67	1.76	1.84	1.93	2.03
7. estimated total market ($)	45.00	49.00	55.00	60.00	66.00	73.00
8. estimated market share (%)	0.10	0.20	0.50	1.00	5.00	10.00
9. estimated market share (units)	0.002	0.003	0.008	0.018	0.096	0.203
10. estimated prophylactic market share ($)	0.056	0.088	0.248	0.590	3.28	7.30
11. total estimated market share ($)	17.00	36.00	98.00	215.00	299.00	401.00

Table 11c

Estimated Market Share

Neisseria meningitidis

	Year				
	8	9	10	11	12
	(numbers in millions)				
Therapeutic Market					
1. estimated total market (units)	2.46	2.70	2.90	2.98	3.31
2. estimated total market ($)	364.00	418.00	480.00	510.00	596.00
3. estimated market share (%)	4.00	8.00	20.00	40.00	50.00
4. estimated market share (units)	0.10	0.21	0.60	1.19	1.65
5. estimated therapeutic market share ($)	14.60	33.50	96.00	203.80	298.00
Prophylactic Market					
6. estimated total market (units)	0.57	0.60	0.64	0.66	0.70
7. estimated total market ($)	17.00	18.60	21.40	22.70	25.10
8. estimated market share (%)	0.10	0.20	0.50	1.00	5.00
9. estimated market share (units)	0.001	0.001	0.003	0.007	0.035
10. estimated prophylactic market share ($)	0.018	0.037	0.106	0.226	1.26
11. total estimated market share ($)	15.00	34.00	96.00	204.00	299.00

Table 11d **Estimated Market Share**

Streptococcus pneumoniae and E. coli

	Year				
	8	9	10	11	12
	(numbers in millions)				
Streptococcus pneumoniae					
Therapeutic Market					
1. estimated total market (units)	0.7	0.73	0.79	0.81	0.85
2. estimated total market ($)	104.00	114.00	130.00	139.00	153.00
3. estimated market share (%)	4.00	8.00	20.00	40.00	50.00
4. estimated market share (units)	0.03	0.06	0.16	0.32	0.43
5. estimated therapeutic market share ($)	4.00	9.00	26.00	55.00	77.00
E. coli					
Therapeutic Market					
1. estimated total market (units)		2.72	2.97	3.06	3.22
2. estimated total market ($)		430.00	493.00	523.00	580.00
3. estimated market share (%)		4.00	8.00	20.00	40.00
4. estimated market share (units)		0.11	0.24	0.61	1.28
5. estimated therapeutic market share ($)		17.00	39.00	105.00	232.00

Table 11e

Estimated Market Share

Klebsiella and Salmonella

	Year			
	9	10	11	12
	(numbers in millions)			
Klebsiella				
Therapeutic Market				
1. estimated total market (units)	0.98	1.05	1.08	1.14
2. estimated total market ($)	152.00	174.00	185.00	205.00
3. estimated market share (%)	4.00	8.00	20.00	40.00
4. estimated market share (units)	0.04	0.08	0.216	0.456
5. estimated therapeutic market share ($)	6.15	13.90	37.00	82.10
Salmonella				
Therapeutic Market				
1. estimated total market (units)	1.24	1.33	1.32	1.44
2. estimated total market ($)	192.00	221.00	234.00	260.00
3. estimated market share (%)	4.00	8.00	20.00	40.00
4. estimated market share (units)	0.05	0.11	0.27	0.58
5. estimated therapeutic market share ($)	7.70	17.70	46.90	103.70

broken down into therapeutic and prophylactic segments in Table 11f. The market share to be obtained by the Company's products for therapeutics in years 7, 8, 9, 10, 11 and 12 are 4%, 8%, 20%, 40%, 50% and 60%, respectively. These percentages represent the share obtained for each new drug starting from its first year on the market which, for drugs rAb 1 and rAb 2, will be in year seven. The reason for the expected aggressive market share penetration is due to the long (two to three year) R&D phase and long (three to four year) clinical research phase, at which time the markets (hospitals and physicians) are being informed of the potential new drugs. There is a great deal of market awareness by the time the product reaches the market. The Company's estimate of the prophylactic market share is represented by much lower numbers, 0.1%, 0.2%, 0.5%, 1.0%, 5.0%, 10.0%, in years 7-12, repectively. This is due to a presumed lower usage in prophylaxis as compared to therapeutics. The reason for this is that antibiotics (competitive product) have a broader spectrum of antibacterial activity.

The Company expects to gain first to the market advantages (38) on its products, but anticipates increased competition in later years. The total estimated market share is listed in Table 11g. Sales revenues for year one of product sales (year seven of company's lifetime) is $32.9 million. The second, third, fourth, fifth and sixth year sales are $89.0 million, $267.4 million, $619.8 million, $1007.3 million and $1642.2 million, respectively. These figures represent the introduction of the Company's proposed first seven products into the market. These figures represent total sales revenue should the Company manufacture and market its own products. However, since the Company plans on establishing joint ventures for manufacturing and marketing, it might expect to obtain about 10% of these revenues as royalties (Table 11g).

Table 11f

Estimated Markets
(numbers in 1000's)

Bacteria	Total Market ($)	Total Market (units)	Therapeutic Market (units)	Prophylactic Market (units)
Pseudomonas aeruginosa	$422,630.0	13,416.7	1,928.7	11,488.0
Haemophilus influenzae	225,980.0	3,164.6	2,033.6	1,131.0
Neisseria meningitidis	81,970.0	2,130.0	1,742.1	388.0
Streptococcus pneumoniae	78,330.0	642.0	473.5	169.0
Escherichia coli	178,700.0	1,787.0		
Klebsiella	63,370.0	630.0		
Salmonella	80,000.0	800.0		

legend: One unit refers to one dose. A therapeutic dose consists of 100 mg injections and a prophylactic dose refers to one 25 mg dose.

Table 11g

Total Estimated Market Share
(for all products listed in Tables 11a-e)

	Year					
	7	8	9	10	11	12
	(numbers in millions)					
Total estimated market share ($)	32.90	89.00	267.40	619.80	1007.30	1642.20
Total estimated market share, 10% royalties ($)	3.29	8.90	26.74	61.98	100.73	164.22

IV. Marketing Plan

IV.A. General Characteristics of the Pharmaceutical Market

The market that the Company's products will be in is the pharmaceutical market which includes human diagnostics. In the U.S. (and other industrialized countries) an oligopolistic market structure exists for each new therapeutic drug class. Consumers may purchase specific drugs by prescription only. The market demand is unique in that consumers, having chosen the option of health care, will purchase the drugs under the direction of physicians. Superior drug quality rather than price dominates this market. Overall success for individual companies depends on having a few successful products in some market segments. The quality of research and development (R&D) is a key factor in this industry. R&D productivity drive product innovation and differentiation which is the basis of competition in the pharmaceutical industry.

In the U.S. a new drug takes from six to ten years to develop and costs about $60-80 million dollars. This is due in large part to the extensive clinical trials and regulatory process required by the Federal Drug Administration (FDA), one of the governmental regulatory agencies (35). The pharmaceutical industry tends to be dominated by a small number of large firms worldwide as a result of the huge R&D investment required to bring a new drug to the market.

Also falling under the pharmaceutical market category are *in vitro* diagnostics. Diagnostics, as opposed to therapeutics, require less investment and R&D because compliance with regulatory requirements is far less expensive. As a result, diagnostic products can be marketed fairly rapidly. Many companies have entered the diagnostic market in response to this.

IV.B. Overall Marketing Strategy

The Company's product groups are targeted at distinct markets:

1. In vivo therapeutic market
2. In vivo prophylactic market

The Company will not initially market its own products. It will enter into joint ventures with one or more pharmaceutical marketing companies to market and manufacture the Company's products. These collaborations will allow the Company to establish an early worldwide market position and reach a large number of geographically diverse customers, while concentrating on product development. Eventually the Company may decide to manufacture and market its own products.

To assure a market success the following four points are essential:

1. Be first to human clinical trials and market.
2. Test and offer a number of rAb's before our competition does so.
3. Establish a proprietary patent position by maximum pursuit of substance of matter patents and process patents, and possible defense of these.
4. Use international partners to maximize both preclinical and clinical data in the least time with fewest resources.

A strong marketing position will be established as the Company's products offer a major consumer benefit that the competition cannot match. Because of the Company's products ability to overcome bacterial antibiotic resistance, the consumer benefits, in some cases, will be the dramatic result of life over death.

In regards to the in vitro diagnostic market, should the Company develop any useful reagents as a side product of its efforts in therapeutic development, it will look to enter into joint venture arrangements. The Company will provide the antibodies themselves as reagents to the joint venture partner. In some cases, the Company might decide to sell outright the entire antibody and patent rights to another company, who may decide to further develop the diagnostic product.

Companies with which the Company will consider establishing joint ventures with for the development and production of mAb diagnostics includes: Abbott Labs, Bayer, Bristol-Myers, Eli Lilly, Merck, Hoffman LaRoche, Pfizer, Squibb and others (any company involved with infectious disease, producing antibiotics or diversifying into the infectious disease market).

IV.C. Pricing

The demand curve for the Company's products will be largely inelastic, due primarily to the nature of the products themselves. The prescription drugs are vital to health, and within reasonable limits, will be purchased in spite of price increases. In addition, there will be little reason for purchasing more of the drug than is needed regardless of how much the price decreases. Price becomes a secondary consideration in purchase, as the physician plays a major role as the decision maker in the choice of prescription drugs. Furthermore, the efforts of the Company toward product differentiation reduces the importance of price as a consideration in drug choice and therefore reduces the elasticity of demand.

The joint venture company that manufactures and markets the Company's products should try to maintain the pharmaceutical industry norm of 80% gross margin.

Current cost of antibiotic therapy ranges from $15-400 per day per patient, and can be higher (48). The Company has estimated sales of its therapeutic products at $100 per therapeutic treatment and $20 per prophylactic treatment. Both the therapeutic and prophylactic treatments are expected to require a single dose (injection). These prices may be significantly underrated and in some cases may be 4-20 fold higher.

IV.D. Sales Tactics

Sales of the Company's products will be carried out by the manufacturer or marketing joint venture partner. A general sales tactic for the Company's products would include: a) at first, a relatively small sales force which could contact the internal medicine and infectious disease units at hospitals in the U.S. and speak to the specialty physicians and, b) a larger sales force would be necessary to include other specialty physicians falling under the product's particular prophylactic mode (i.e., major surgery, haematologic disorders, etc.).

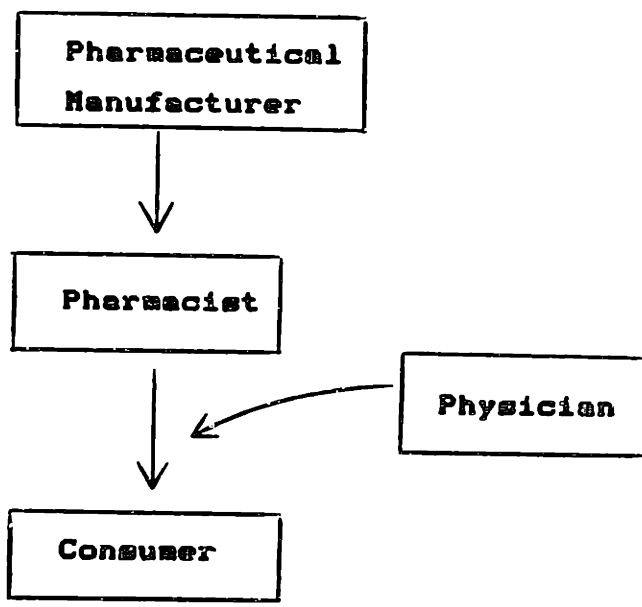
IV.E. Advertising and Promotion

The Company would attend and make presentations at trade shows and advertise nationally and worldwide in recognized journals such as the New England Journal of Medicine, The Journal of the American Medical Association, The Lancet, The American Journal of Medicine and other specialty infectious disease journals.

The main feature of the Company's products that will be emphasized to generate sales will be the quality and uniqueness of the product(s). In many cases the products will fill a market need where there is currently no available product.

IV.F. Distribution

With regards to its therapeutic products, the Company will seek joint venture partners with distribution strengths in the appropriate market segments. A typical channel of distribution for the Company in the prescription drug field would look like:



The law requires that a physician is the intermediary decision maker between the manufacturer of the prescription drugs and the consumer. The Company's products are ethical pharmaceuticals and can only be sold by prescription for administration by physicians. Therefore, they must be sold directly to the pharmacies. This obviates the need for wholesalers.

The major pharmacy customers for the Company's products represent hospital retail pharmacies. The reason being is that the Company's products are administerable by injection only under the care of a physician. The Company's products would most likely not be carried by a local pharmacy. A smaller group of customers would be the physicians themselves.

The marketing division of the Company must also focus on direct sales to hospitals, as the Company may hope to attain exposure to physicians in exchange for better contract prices. The differential price to hospitals may be viewed as a marketing expense. Physicians represent potential future purchasers (prescribers) in the marketplace.

The selling of pharmaceuticals to the government institutions closely parallels selling to the non-governmental hospital segment of the market.

V. Design and Development Plans

V.A. Development Status and Tasks

The Company will commence into the very early stage of product development. The Company's success in developing a marketable therapeutic product within seven years lies in the licensing of mAb's to infectious disease agents currently available from various universities. The Company will begin immediate in-house development of rAb's from the licensed mAb's, to be used as both therapeutic and prophylactic agents. The Company will concurrently begin developing, in-house, mAb's (human and mouse) to infectious disease bacteria. These Company owned

mAb's will then be converted to rAb's for therapeutic and prophylactic drug use. The product development involves the following:

1. Production of mAb's (human and murine) to infectious bacteria.
2. Isolation and cloning of the Ab genes.
3. Construction of human and human/murine chimeric rAb's.
4. Construction of rAb expression vectors for production in mammalian cells.
5. Expression of rAb's in mammalian cells.
6. Testing of the rAb's for treatment and protection of infectious disease in animal models.

A list of rAb development steps is given in Table 12. The primary steps (I) outline what needs to be done immediately. The key issues (II) are the following steps to take. The next steps IIIA, is crucial for future Company development. Next steps IIIB, reflects the importance of getting the Company into the European market, and IIIC and IIID refer to issues the Company needs to become intimately involved with should it choose to manufacture and market its own products.

All the required R&D technologies will be set up in-house. The Company is dependent in its research efforts upon the scientific team headed by Dr. Glenn E. Nedwin, President and Director of Science of the Company. The Company's success in developing marketable products and achieving a competitive position will depend, in part, on its ability to attract and retain qualified scientific and management personnel.

Table 12 rAb Development Steps

I (primary step)	II (key issues)	III (next steps)
A. Clone and express antibody gene heavy and light chains	A. Choose gene expression system based upon pharmacological, manufacturing and patent data	A. Continue and expand the evaluation of alternative expression systems
B. Sign joint venture agreement with manufacturing and marketing partner	B. Develop and coordinate R&D process development, pre-clinical and funding strategies for each rAb	B. Complete project funding arrangements, identify European joint venture partner
C. Recombinant antibody purification	C. Choice of recovery process; based upon estimated cost, time for completion and regulatory issues	C. Determine the regulatory and manufacturing issues involved with rAb product
D. Initial *in vitro* and *in vivo* animal model testing of rAb	D. Initiate rAb efficacy studies in selected *in vivo* animal models	D. Detail the clinical strategy and coordinate with pre-clinical pharmacological studies

V.B. Difficulties and Risks

V.B.1. Risks of Focussed Products Strategies

A threat to all new companies, regardless of their type of strategy, is that once a new pioneering company has taken all the risks, i.e., once the technical and commercial feasibility of a new technologically produced product has been established, a larger more established company may devote large resources to develop that product. The policy of freely publishing scientific results is an additional potential problem in the biotechnology industry. This can remain a problem in spite of pre-filing patent applications. Publishing of results enables the more established firm to jump in, either at the first generation with a "me-too" product, or to develop a second generation product at substantially lower cost. However, superior market price is not the best strategy in the pharmaceutical industry but rather superior products.

The above scenarios, while they may be attempted, do not appear to be too threatening to the Company due to the complex technology and personnel expertise required to "discover" and develop the Company's particular products. The technology in this industry is labor intensive and requires skilled hands to "make it happen."

Focused product niches may dislocate the firm's present and future (expected) resources and the market it is aiming at. For many new biotechnology companies, it is hard to raise sufficient funds to achieve forward integration into a fully independent pharmaceutical manufacturing company. With the rapidly changing scientific and technologic environment, too much focus is bad and very risky, leading to overspecialization. This does not present a problem for the Company as the antibody

technology allows a vast expansion into related targets (see II. C. 3). Due to lack of patents on the basic monoclonal antibody technology and lower entry barriers, the diagnostic field has become very competitive, especially in the area of cancer diagnostics. If companies use this type of strategy to an extreme, they will miss out on the potentially more valuable products such as therapeutics, prophylactics and imaging.

V.B.2. Product Risks: mAb's Amenable to Therapy

The first requirement in the production of mAb's (or rAB's) against infectious bacteria as a product is the demonstration of Ab-mediated protection. This involves the production of Ab's that can cause the destruction of the bacteria by one of several immune response mechanisms (see figure 4). Bacterial species usually possess several antigenically specific cell surface molecules (usually lipopolysaccharides as the antigens) that confer specific immunity. Thus it will be of major importance to develop mAb's that can react with all antigenically varied species of a particular bacteria. This may pose a problem for some bacterial strains and as a result the Company will need to develop a few different mAb's to cover a particular strain.

If this occurs, it introduces a major complexity involved with the clinical testing, i.e., the testing of a mixture of drugs. This would result in added clinical costs. On the other hand, the extremely competitive and rapid development of antigenically strain specific diagnostic tests that is occurring may circumvent the need for multiple drug clinical trials. The reason being that if a particular "subtype" of bacterial strain could be quickly identified, the correct therapeutic could be immediately chosen, rather than having to administer a drug mixture.

V.B.3. Risks in Manufacturing

The development of the Company's products will most likely be a question of economics rather than science. The Company's products must be produced by mammalian cells. In the past, large scale culture of mammalian cells has proven to be very difficult and expensive (49). Current and ongoing advances in biochemical engineering on bioreactor design (growth chamber and mechanics of mammalian cell culture system) have achieved some large scale-up operations. Due to the Company's large amount of products required per year, 24,000-938,000g/yr (Table 13) the ability of efficient large scale production will become increasingly important. The development of a cost effective process is a vital aspect of the Company's future profitability.

Typically mammalian cells are cultured in serum derived from fetal calves. This serum contains many of the growth nutrients required for cell growth, including hormones, vitamins, essential small molecules and growth factors. However, commercially available serum is expensive and batch to batch variable. A typical cell culture medium contains approximately 10% serum. The Company will strive to adapt their cell lines to grow in a lower percentage of serum. Many cell lines have been adapted to grow in one percent serum. The Company will also strive to develop cell lines that grow in the absence of added serum.

A more costly approach would entail chemically defining the manufacturing process. The chemically defined media, however, will have to be supplementd with exogenous growth factors. The benefits are that this ultimately leads to an easier regulatory approval. It may be advantageous at some point for the Company to develop in-house some of the raw materials necessary for cell

Table 13

Production Requirements

	Year (units in millions) (grams in thousands) 7	8	9	10	11	12
1. Pseudomonas						
a. therapeutic (units/yr)	0.11	0.23	0.60	1.26	1.65	2.08
b. therapeutic (grams/yr)	11.10	23.00	60.00	126.00	165.00	208.00
c. prophylactic (units/yr)	0.02	0.04	0.09	0.19	0.99	2.10
d. prophylactic (grams/yr)	0.40	1.00	2.25	4.75	24.75	52.50
2. Haemophilus						
a. therapeutic (units/yr)	0.12	0.24	0.63	1.32	1.73	2.19
b. therapeutic (grams/yr)	12.00	24.00	63.00	132.00	173.00	219.00
c. prophylactic (units/yr)	0.002	0.003	0.008	0.018	0.10	0.20
d. prophylactic (grams/yr)	0.05	0.075	0.20	0.45	2.50	5.00
3. Neisseria						
a. therapeutic (units/yr)		0.10	0.22	0.58	1.20	1.70
b. therapeutic (grams/yr)		10.00	22.00	58.00	120.00	170.00
c. prophylactic (units/yr)		0.006	0.012	0.032	0.066	0.35
d. prophylactic (grams/yr)		0.15	0.30	3.20	1.65	8.75
4. Streptococcus						
a. therapeutic (units/yr)		0.03	0.06	0.16	0.32	0.43
b. therapeutic (grams/yr)		3.00	6.00	16.00	32.00	43.00
5. E. coli						
a. therapeutic (units/yr)			0.11	0.24	0.61	1.28
b. therapeutic (grams/yr)			11.00	24.00	61.00	128.00
6. Klebsiella						
a. therapeutic (units/yr)			0.04	0.08	0.22	0.46
b. therapeutic (grams/yr)			4.00	8.00	22.00	46.00
7. Salmonella						
a. therapeutic (units/yr)			0.05	0.106	0.274	0.576
b. therapeutic (grams/yr)			5.00	10.60	27.40	57.60
8. Total (grams/yr)	23.60	61.20	173.75	383.00	636.30	937.90

note: one therapeutic unit = 100 mg.
one prophylactic unit = 20 mg.

growth. Alternatively one could establish a joint venture or contract from a small supplier of such materials.

V.B.4. Critical Risks

The dose required to treat a patient could be significantly higher or lower, which would have an effect on increasing or decreasing the cost of goods sold. While this directly affects the manufacturer, the Company could be affected by altered cash flows (negatively or positively).

V.C. Product Improvements and New Products

An important feature for companies with a "focused" strategy has been in planning for technological discontinuities (37) even before their first products come onto the market. Genetically engineered protein therapeutic products represent the "first" generation products. Almost all the new biotechnology companies have already begun production of the future generation products which involve a range of technologies including genetic techniques and protein engineering (50). The investment in protein engineering gives the companies the ability to compete in the 2nd, 3rd, etc., generation products. This is a very interesting characteristic of the emerging biotechnology companies. They have the need, insight and willingness to develop multiple scientific approaches on similar products simultaneously. This occurs before the first product reaches the market, well before reaching its growth and saturation points. Recognizing this early will give the new biotechnology firms a tremendous competitive advantage. This is very uncharacteristic of

the larger, established companies (pharmaceutical and chemical).

The Company, through the rDNA technology, will be able to expand its development of rAb's very early on. Before the first therapeutic Ab is on the market, the Company will be developing "altered" molecules with superior characteristics. These altered characteristics will include increased Ab efficacy and mechanism of production. The same Ab's used for therapeutic and prophylactic use may be later developed for diagnostic in vivo imaging potential.

VI. Manufacturing and Operations Plan

VI.A. Geographic Location

The geographic location of the Company will be in the San Francisco Bay Area. The advantages of such a location is the close vicinity to the University of California at San Francisco, Berkeley, Stanford University and numerous other academic institutions. These universities and the numerous biotechnology firms in the Bay Area, represent a rich source of highly trained and qualified staff from which the Company can draw upon. Additionally, the attractive climate and cosmopolitan flavor of the area is conducive for attracting and keeping qualified staff.

VI.B. Facilities and Capacity Improvements

The Company will lease furnished laboratory space for $14.00 per square foot/year. The research labs and office will require approximately 6,000 square

feet, which will be able to accomodate 26 total employees comfortably (5,000 sq ft for labs, 1,000 sq ft for offices). The lease costs have a $ 50,000, year one expense in order to make minor alterations to the leased lab space.

VI.C. Manufacturing Strategy

VI.C.1. General

The Company does not initially intend on manufacturing its own products. There are several commercial manufacturers who specialize in mammalian cell culture and product manufacture. The Company will investigate potential joint ventures in this area. One particular company, Invitron, Inc. (St. Louis, MO), will be considered due to their vast experience in mammalian cell culture and production of antibody proteins of FDA quality. Others include Damon Biotech (Needham, MA), Celltech (U.K.) and Bioresponse (Oakland, CA). However, the manufacturing strategy formulation discussed below will be used should the Company decide at a later date to manufacture its own products. The goal of the Company is to develop, manufacture and market (alone or in joint venture) products of extremely high purity. The products manufactured by the Company represent new molecular entities and substances that are extremely rare and costly to obtain. Many genetically engineered health care products can be produced by fermentation of microbial systems (growth hormone, insulin). However, the Company's products, recombinant antibodies, need to be produced in mammalian cells due to their complexity. The rAb's will be synthesized from raw materials by mammalian cells that have been genetically altered to perform the synthesis. The mAb's will also be

synthesized from raw materials by their natural cell source. Mammalian cells are generally more difficult to grow than bacterial microorganisms (classical fermentation) due to their larger, more complex size and lack of rigged walls. The manufacturing of these products will require a highly specialized facility operated by individuals skilled in molecular biology and tissue culture cell growth. The following manufacturing strategy includes the requirements for a manufacturing facility (51).

These requirements include that the facility is:

1. capable of generating and supporting mammalian tissue culture (52) that can generate the desired antibody product(s);
2. capable of recovering and purifying these products from the growth conditions, ie., cell suspension, cell perfusion;
3. capable of packaging the products according to Good Manufacturing Practices (GMP), able to meet variable production demands, staffed with a highly skilled workforce;
4. registered with the Food and Drug Administration (FDA).

An overall strategy for mammalian cell culture is outlined in Thilly (52). At present, production of products in mammalian cells is done on an empirical basis. The rules and requirements, as a function of nutrients and metabolic products, have not yet been written for mammalian cell growth as has been done for microbial fermentation (53). The mechanics and mathematical growth characteristics of mammalian cells in culture has only recently begun to be addressed (54).

The strategy for overall productivity must include an examination of the product of interest, the particular cells, the cellular environment and the fermenter parameters. The specific approaches on each parameter will depend critically on the product desired. The fundamental problems of genetic, cellular and biochemical engineering of high volume (greater than 1000 liters), high density mammalian cell cultures is only recently being addressed in practice (52).

VI.C.2. Mammalian Cell Culture: rAb Production

The yearly manufacturing requirements for rAb production, starting in year seven, are outlined in Table 13. Year seven is the first year (estimated) of product sales, as a result of FDA marketing approval. The rAb yearly production requirements are: year seven, 23,600 grams; year eight, 61,200 grams; year nine, 173,750 grams; year ten, 383,000 grams; year 11, 636,300 grams; year 12, 937,900 grams. Year seven reflects the marketing launch of the Company's first two rAb's; year eight, launch of the third and fourth rAb's; year nine, launch of the fifth, sixth and seventh rAb's. The Company will require additional rAb's for pre-clinical and clinical trial testing. This should amount to approximately 10-100 grams of antibody for in vitro and animal model testing and 100-1000 grams of antibody for each phase of clinical trials.

The capabilities of producing large quantities of rAb's is outlined in Table 14. The specific production capability will depend on the concentration of secreted rAb from the individual cell lines. Typical Ab production rates range from 1-200 micrograms per milliliter (ug/ml), with 50 ug/ml the average. A theoretical calculation of the varying specific rAb productivities and production

Table 14

Recombinant Antibody Production: Mammalian Cell Culture
Theoretical Calculations

1. rAb product ug/10^6 cell/ml·day	1	10	50	100	200
2. % cell protein	0.1	1.0	5.0	10.0	20.0
3. stirred tank system: rAb product					
a. ug/10^6 cell/ml·day	10	100	500	1000	2000
b. g/2000 l·day	20	200	1000	2000	4000
c. g/10,000 l·day	100	1000	5000	10,000	20,000
4. Perfusion system rAb product					
a. ug/$5x10^7$ cell/ml·day	50	500	2500	5000	10,000
b. g/2000 l·day	100	1000	5000	10,000	20,000
c. g/10,000 l·day	500	5000	10,000	50,000	100,000

1. assume total cell newly synthesized protein = 1 ng/cell day (47).
2. stirred tank system reference (55).
3. perfusion system reference (56).
4. ml, milliter; l, liter; ng, nanogram; ug, microgram

volumes in a stirred tank (55) and in a perfusion system (56) are shown in Table 14. Theoretically, one 10,000 liter stirred fermenter could produce approximately 5,000 grams of Ab per day (50 ug/ml) and one 10,000 liter perfusion reactor could produce 10,000 grams of Ab per day.

An example of some experimental results from the perfusion system is given in Table 15 (56). At secretion of 50 ug/ml, one could make approximately 100,000 grams of antibody in 180 days using one 10,000 liter reactor (fermenter). Using this figure, a calculation of the estimated production schedule is shown (Table 15). The production schedule assumes an 80% final product recovery rate. In year seven it would require one 10,000 liter reactor operating 53 days to yield the (purified) 23,600 grams of rAb needed for marketing. By year 12 the Company would require the equivalent of ten 10,000 liter reactors to produce the necessary antibody levels (937,900g). As a practical example, a contract manufacturing company like Invitron, Inc. (St. Louis, MO), has the capacity to produce approximately 70,000 grams of Ab using 1.3 million liters of culture medium in their first existing plant (56).

By increasing the specific rAb productivity (amount rAb secreted by each cell), by cellular and molecular approaches, one can expect to decrease the production volumes and costs (by a factor of 10-50 fold). For most bacterial diseases the levels of antibodies required in the serum to confer significant protection are in the microgram/ml range or lower. This would indicate that milligram injections (i.e., 10-200 milligrams/patient) of certain rAb's would be sufficient. If this were the case, then the yearly production requirement could be 10 to 40 fold lower. As mentioned above, the actual manufacturing results will depend on addressing genetic, cellular, and biochemical engineering aspects of high volume, high density mammalian cell culture (52).

Table 15

Estimated Production Schedule

	Year					
	7	8	9	10	11	12
1. Production required (g/yr) (no's in 1000's)	23.6	61.2	173.8	383.0	636.3	937.9
2. Production required (g/yr) (no's in 1000's) assume 80% final product recovery	29.5	76.5	217.3	478.8	795.4	1173.4
3. No. days production using a 10,000 l reactor (no. of reactors required in parentheses)	53 (1)	138 (1)	195 (2)	216 (4)	238 (6)	211 (10)

note: (1) x 10,000 l reactor for 180 days= 150,000 l media containing 100,000 ug Ab.

Perfusion System:

rAb product

50 ug/10^7 cells ml

g product/40 l·18 days = 40 g
g product/2000 l·18 days = 200 g
g product/1,000 l·18 days = 10,000 g
g product/10,000 l·180 days = 100,000 g

VI.C.3. Manufacturing Facility Requirements

The manufacturing facility should have the following requirements:

a. Only antibody products will be manufactured at the facility. This will provide some economies of scale, as all products will be of antibody nature.
b. The plant capacity and annual requirements will be outlined according to production schedules (i.e., Table 15).
c. The manufacturing facility will not produce its own raw materials and specialty chemicals. Sources will be identified for these materials. (see manufacturing risks, section VI.B.3)
d. A pilot plant space allocation will be made.
e. The geographical location of the manufacturing facility will be near major universities and other related companies so there will be access to a skilled workforce.

VI.C.4 Manufacturing Alternatives

Important factors that will influence the manufacturing decisions include:

a. The amount of capital available for investment in facilities and equipment.
b. The stage of development of the processing technology required for manufacturing.
c. The quantity of finished goods required.
d. Product launch date.
e. Availability of raw materials, intermediates and packaging materials.
f. Knowledge of current Good Manufacturing Practices (GMP), as the products will be pharmaceuticals.

Manufacturing alternatives include:

a. Manufacturing the raw materials or key intermediates needed for product synthesis.
b. License the product or process to outside firms.
c. Choice of mammalian cell culture technology i.e., airlift fermentation, suspension, anchorage, perfusion.
d. Arrangement with another firm, whereby they provide manufacturing assistance in exchange for R&D assistance.
e. Acquisition of an existing manufacturing facility.

VI.C.5. Time Table for Reaching Key Milestones

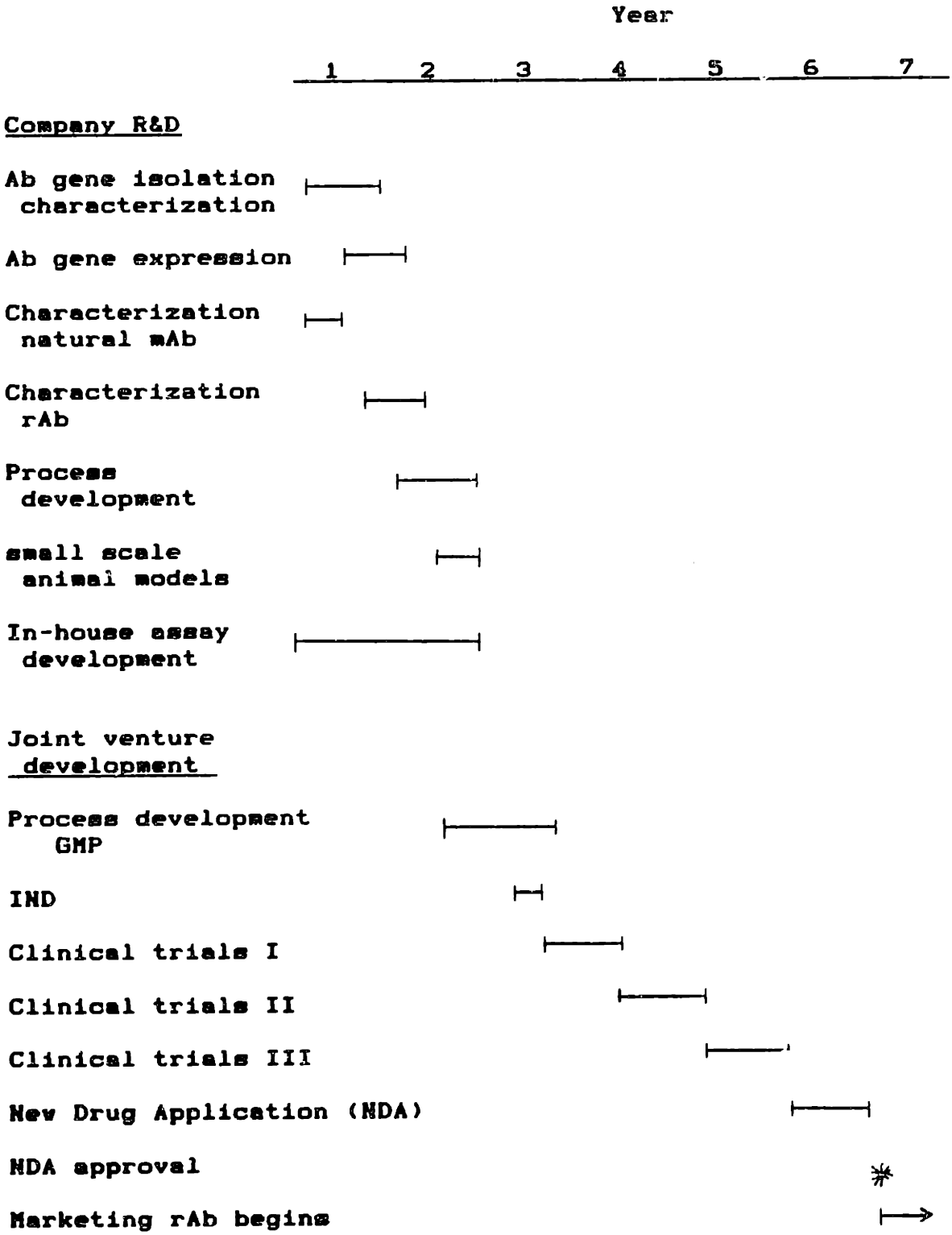
a. The first and second therapeutic recombinant antibody should be ready for launch approximately seven years from the Company starting date.
b. The second and third therapeutic recombinant antibody should be ready for launch approximately eight years from the Company starting date.

The key milestones concerning the entire drug development project are outlined in Table 16.

The Company expects a two year time horizon for the in-house R&D leading to a therapeutic drug ready for further development by the joint venture partner. This assumes obtaining a license for its first and second mAb to take through its rAb R&D process. For in-house R&D on its own mAb's and rAb's the Company expects to add on another year into the drug development time horizon (three years). The Company will develop in-house mAb's concurrently with licensed mAb development. This will enable the Company's own products to be marketable by year eight.

Table 16

Drug Development Milestones



A key factor to manufacturing will be the knowledge of industrial fermentation, specificially industrial mammalian cell tissue culture, and knowledge of the pharmaceutical industry.

The fermentation facility will of necessity be a complex manufacturing unit. It will be designed to grow the recombinant mammalian cell and recover and purify the specific antibody products. The operation of such a facility will require a highly trained workforce consisting of biochemical engineers, operators and a maintenance staff. The capital investment required to erect a manufacturing facility can range from $5M-$100M, depending on the plant capacity and the complexity of the recovery and purification processes (57,58). An average cost for a manufacturing facility like the one needed by the Company is approximately $30-40 million.

In formulating a manufacturing strategy it will be very important to have a working knowledge of the pharmaceutical industry, specifically the regulatory issues and environment in which it operates. The requirements are promulgated by the FDA. In the area of pharmaceuticals, the GMP's are of primary importance. The GMP covers guidelines for design of equipment and facilities, process validation, ongoing training of personnel, control of raw materials and packaging, production and process controls, holding and distribution of finished goods, laboratory controls and records and reports. The necessity of following the current GMP "to the letter" cannot be overemphasized, as failure to do so could result in costly delays in the commencement of manufacturing.

VI.C.6. Regulatory and Other Compliances

The products under development by the Company are intended for use in humans. They are therefore subject to rigorous preclinical and clinical testing and approval processes by the FDA and similar health authorities in other countries. The FDA's office of Biologics Research and Review administers the regulatory approval process for mAb based and rAb based products. This process is similar to that for any new drug product for human use.

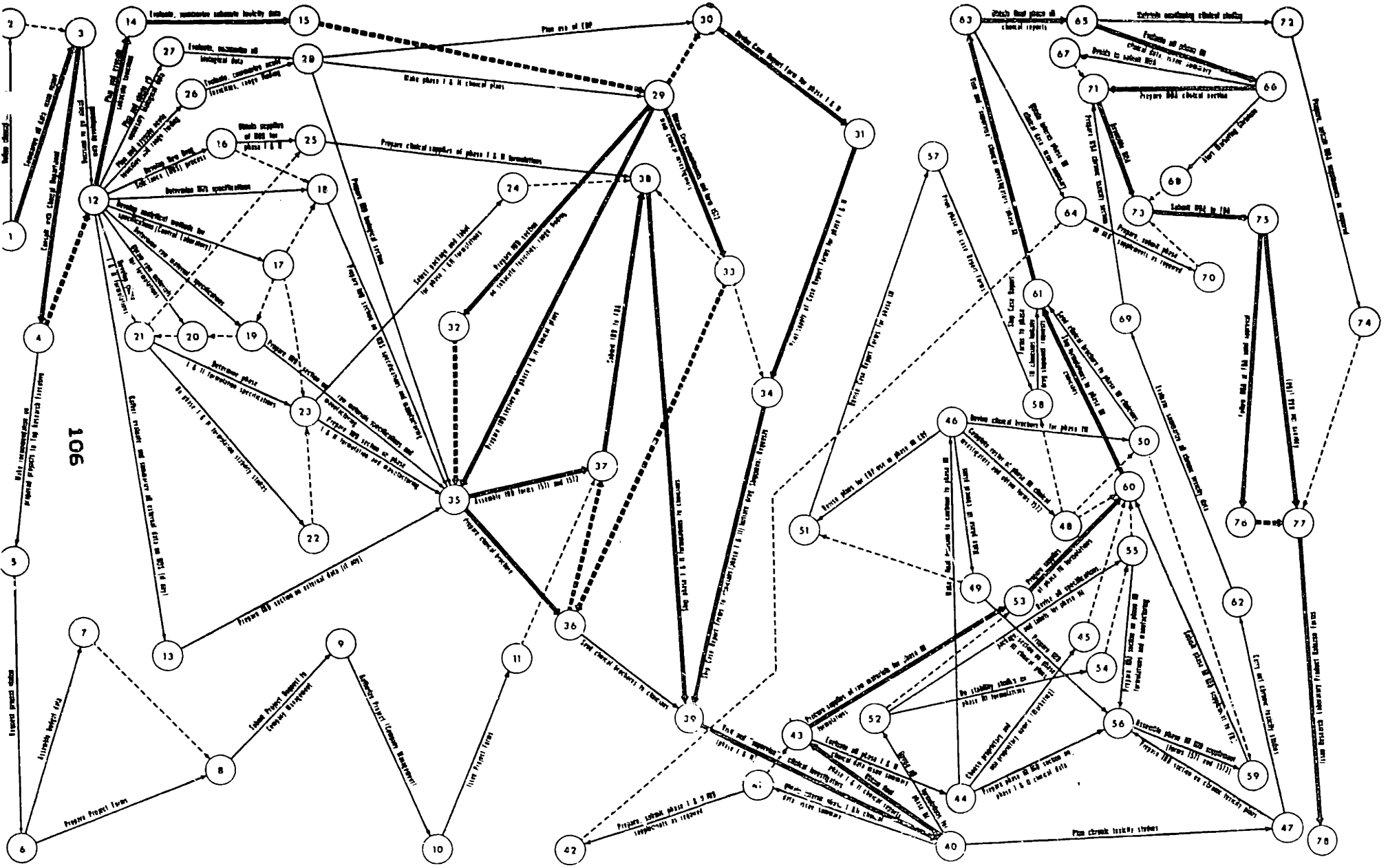
The requirement for approval of a new drug or biologic typically involves a three phase process of pre-market testing.

Phase I clinical trials: testing for the safety and tolerance of the drug with a small group of patients; it may also yield preliminary information about the effectiveness of the drug and dosage levels.

Phase II clinical trials: testing for efficacy, determination of optimal dosage and identification of possible side-effects in a larger patient population.

Phase III clinical trials: additional testing for efficacy and safety with an expanded patient population.

The complex operation of the commercial development of a new drug from laboratory identification to market has been documented in outline form (59). An example of the generalized critical path network (CPN) procedure, figure 12, is applicable to the development of all new pharmaceutical products from the time of identification of a potential new drug substance through approval of the New Drug Application (NDA) by the FDA. The "time zero" used in the CPN is defined as the time when all laboratory data has been evaluated and the decision is made by the appropriate personnel to proceed with the development of a new product.



Critical Path Network. The critical path is shown by the heavy arrows.

The FDA may consider applications for marketing approval of products after completion of Phase II efficacy studies when the products are for treating conditions which lack alternative therapies and are life threatening. The Company will be developing several rAb products falling into this category and therefore can expect a decreased time to market for these products. Once the clinical studies have been completed, a product license application (PLA) is submitted to the FDA for product marketing approval and for licensing of the product manufacturing facilities.

VI.C.7. Efficacy and Safety Considerations

It is most likely that the FDA will apply the most stringent guidelines for the acceptability of preparations for human administration. FDA requirements include the production of sterile and pyrogen free solutions of human mAb (rAb) for human administration. The burden of proof that the huAb's are free of: i) tumor viruses, ii) viral oncogenes, and iii) other tumor promoting elements, will fall on the manufacturer of antibodies. Such proof will be required prior to the first clinical trials. However, semi-crude human Ig preps (gamma globulins) have been used in the clinic for many years. Human rAb's and mAb's, derived from a single source, should prove to be more easily quality controlled than with conventional pooled human gamma globulin preparations.

One potential problem that exists with the resulting administration of Ab therapy is the production of anti-allotypic and anti-idiotypic antibodies. This refers to the production of patient Ab's to various regions of the therapeutic or prophylactic administered Ab's. In the case of the Company's prophylactic and therapeutic Ab's to

bacterial infections, this does not represent a significant problem. For many bacterial diseases, protracted treatment would not be necessary, and one or two immunizations would be the only therapeutic intervention required for protection.

In instances where specific huAb's were given for prophylaxis in immunodeficient patients, particularly agammaglobulinemics and severe combined immunodeficient patients, little host response to the administered immunoglobulin would be anticipated. If protracted treatment becomes essential in immunologically competent patients, a battery of human rAb's directed to different epitopes on the bacterial pathogen could be injected in series, each new antibody given only when significant antiidiotypic antibodies against the preceding antibody are detected in the plasma.

VI.C.8. Pharmaceutical Formulations

New product integrity techniques will have to be developed for the rAb based products, as the pharmaceutical formulation of rAb based products is a relatively new field. The manufacturing strategy must include a significant emphasis on the development of appropriate pharmaceutical formulations for its products. These pharmaceutical proprietary formulations are intended to maintain product characteristics and integrity without inhibiting therapeutic or prophylactic effectiveness.

VII. Management Team

VII.A. Organization

VII.A.1. Executive Officers (and Co-Founders)

Name	Age	Title
Glenn E. Nedwin, Ph.D.	31	Founder, President, Director of Science, Director
to be named		Treasurer/Controller
to be named		Director, Business Development

Dr. Glenn E. Nedwin is one of the founders of the Company and will serve as its President, Director of Science, and as a general Director of the Company.

The Treasurer/Controller, to be named, will be an individual with approximately 5+ years of experience in finance, accounting and administration. The CFO may or may not be a certified public account.

The Director of Business Development, to be named, will be an individual with 5+ years of experience in the biotechnology, pharmaceutical field. This indivdual will have had a technical background.

VII.A.2. Scientific and Support Staff

Molecular Biology:

Ph.D. Senior Scientist (2)

B.S./M.S. Scientists (3)

Cell Biology:

Ph.D. Senior Scientist (1)

B.S./M.S. Scientists (3)

Protein Biochemistry:

Ph.D. Senior Scientists (1)

B.S./M.S. Scientists (1)

Support Staff

Glassware Washer (1)

Secretaries (1 full time, 1 part time)

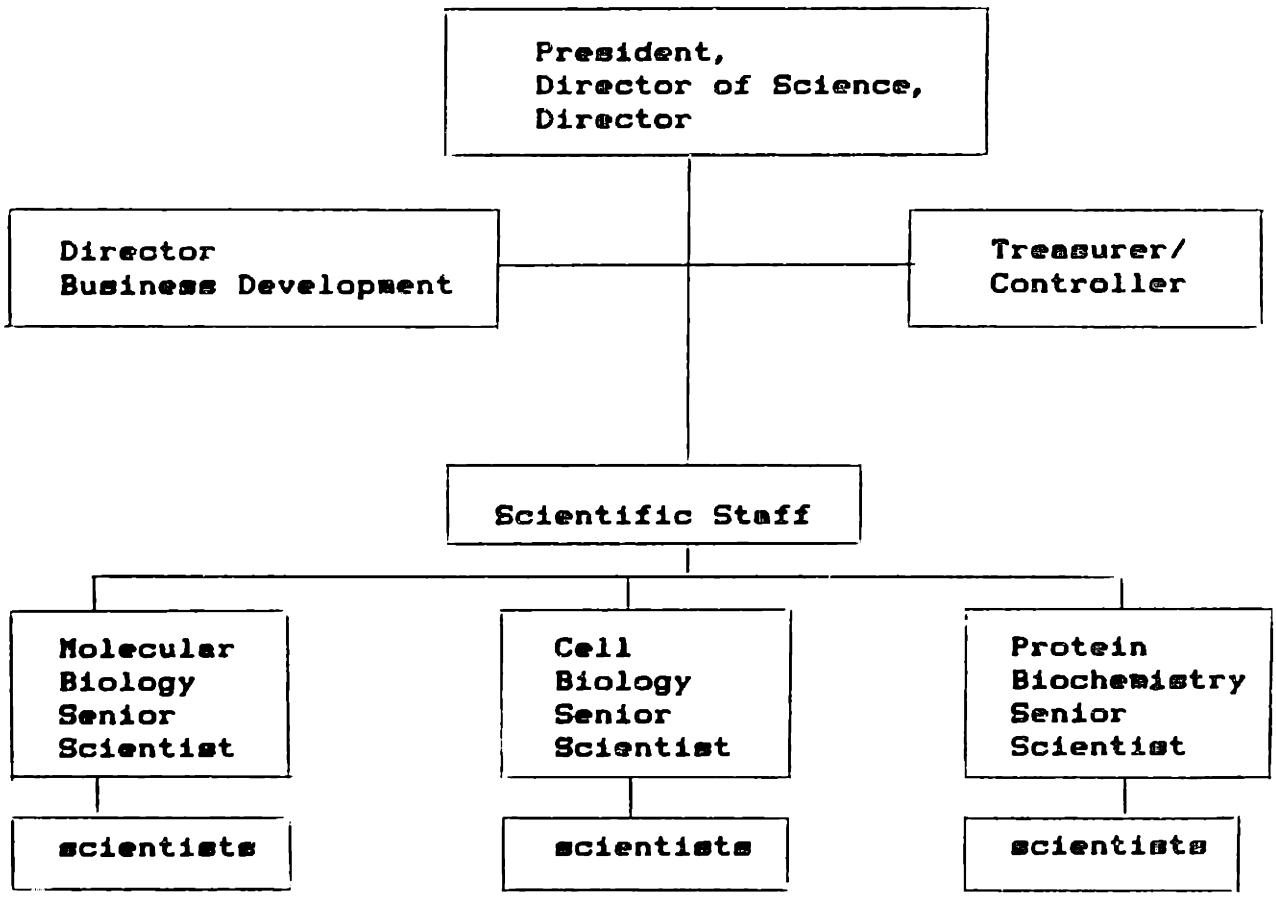
Summary

Executive Officers	3
Senior Scientists	4
Scientists	7
Support	2
Total Employees	16

Table 17 represents the Company's organization in chart form.

Table 17

Organizational Chart



VII.B. Key Management Personnel

Dr. Nedwin will be responsible for the scientific development of the Company. In addition, he will be responsible for the overall general management and direction of the Company. Dr. Nedwin holds a B.S. in Biochemistry (State University of New York, Buffalo), a Ph.D. in Biochemistry (University of California, Riverside) and has worked for three years at Genentech, Inc., a leading biotechnology firm, as a post-doctoral research fellow in the Department of Molecular Biology. He was part of the scientific team that developed two potential anti-cancer therapeutics, human tumor necrosis factor and human lymphotoxin, now in clinical trials. He is a co-author on two patents pending concerning these two therapeutic drugs. Dr. Nedwin also had a major involvement with the start-up of Molecular Therapeutics, Inc., a recombinant DNA based company, wholly owned by Bayer AG. In addition, Dr. Nedwin holds an M.S. (if this business plan/thesis is of any merit) in the Management of Technology from Massachusetts Institute of Technology.

The Treasurer/Controller will be responsible for the financial, accounting and general administration of the company.

The Director of Business Development will be responsible for the commercial licensing of mAb's from various academic institutions and related business aspects of the Company, including marketing and joint ventures.

Scientific Personnel

Molecular Biology: Cloning and expression of rAb's. Technical expertise in: molecular cloning, mammalian expression, DNA sequencing and synthesis.

Cell Biology: Creation and selection of cell lines that produce mAb's, murine and human. Technical expertise in: cell culture, hybridomas, EBV transformations, biological assays.

Protein Biochemistry: Purification and characterization of mAb's and rAb's. Technical expertise in: protein (Ab) purification and characterization.

VII.C. Science and Technology Relationship in the Biotechnology Industry

Competitive advantage and strategy in the Company and in the biotechnology industry has its roots in the special relationship between science and technology (60). Most new biotechnology firms were founded by scientists and are research intensive companies. The environments within are therefore characteristic of university departments with scientific curiosity and freedom (to a lesser extent) abounding. These features have played a major role in attracting first class scientific expertise. Many of the company biotechnologists, interestingly enough, retain their "scientist" affiliation, as they still remain part of the "invisible college" (61). They continue to be reviewed by their academic collegues (albeit in a different manner). This is an area of special concern for the large companies which have not been able to compete with this type of working atmosphere.

In many industries, fundamental research is not essential to an offensive innovative strategy but is often a valuable means of access to new and old knowledge generated outside the firm as well as a source of new ideas within the firm. The Company will definitely use basic research as an essential offensive innovative strategy tool. The Company will also participate in "applications-oriented science". Recombinant DNA and monoclonal antibody technology, the Company's technology base, represents not only the application of biology to industry, but the commercialization of biology itself.

VII.D. Management Compensation and Ownership

Title	Approximate Salary
President	$55,000/yr
Treasurer/Controller	$50,000/yr
Director Business Development	$50,000/yr
Senior Scientist	$50,000/yr
Scientist	$30,000+/yr

VII.E. Incentives

The salaries are commensurate with the industry norms. Due to the fact that this Company is based on its scientific productivity, such salaries and other incentives are required to attract and retain top scientists. The President and Co-founders (treasurer and director of business development) will obtain founder stock commensurate with their initial input (financial, time committment and intellectual). The Company will look for private investors to derive the first year's monies and

possible venture capital as a second source. Specific arrangements will have to be tailor made to fit each investor's requirements with regard to their equity and financial instruments.

The Company will offer stock options on signing for employment for key employees. The Company will also offer an incentive stock option plan to employees based on productivity and performance.

VII.F. Board of Directors

The Board of Directors will intially consist of the President, the other two co-founders and the lead investors. The Company would also like to have an executive member of a hospital (M.D.) on the Board and a top executive of an instrument company.

VII.G. Supporting Professional Advisors and Services

The Company will supplement the efforts of its own scientific staff by identifying and entering into research agreements with academic researchers doing work of interest to the Company. The Company may chose to provide the potential research collaborators with technical and financial support in return for an exclusive license to any resulting technology. These types of licenses have typically required companies entering into such agreements to pay royalties of 2-8% of sales of the company's products that utilized the licensed technology, or one flat fee. The benefit to the company to enter into such agreements is to extend its research capacity and provide access to specialized capabilities.

The Company will also employ a major accounting firm (to be named) and a major legal firm (to be named) on a fee for services basis.

VIII. Overall Schedule

VIII.A. Scientific Personnel

Table 18 shows the five year hiring plan for scientific personnel. Eleven scientific staff members will be optimal for the first year. Since the Company's first two products will be derived from University licenses, the critical staffing will require molecular biologists to conduct the recombinant DNA work and a cell culture biologist.

VIII.B. rAb Drug Development Milestones

Table 19 shows the overall rAb drug development schedule. The development cycle for a rAb is approximately two years. This is the case for the first two products, where the initial mAb's are licensed from university labs. The Company expects to deliver its first two products to its joint venture partner or licensee for further drug development by the beginning of year three. For in-house mAb and rAb drug development the cycle is three years (Table 20). The Company will begin in-house mAb development simultaneously with the first two projects. This will lead to development of its third rAb product. The third product is expected to be delivered by the beginning of year four to the Company's partner or licensee for further development. The steps in the drug development cycle which will be carried out by the joint venture partner or licensee are outlined in Table 20.

Table 18

Scientific Personnel (total)

	Year (number of people)				
	1	2	3	4	5-12
Molecular Biology:					
Ph.D., Sr. Scientists	2	2	2	2	2
B.S./M.S. Scientists	3	6	7	7	7
Cell Biology:					
Ph.D., Sr. Scientists	1	1	1	1	1
B.S./M.S. Scientists	3	5	6	6	6
Protein Biochemistry:					
Ph.D., Sr. Scientists	1	1	1	1	1
B.S./M.S. Scientists	1	2	2	2	2
Support	2	4	4	4	4
Total	13	21	23	23	23

Table 19 rAb Drug Development Schedule

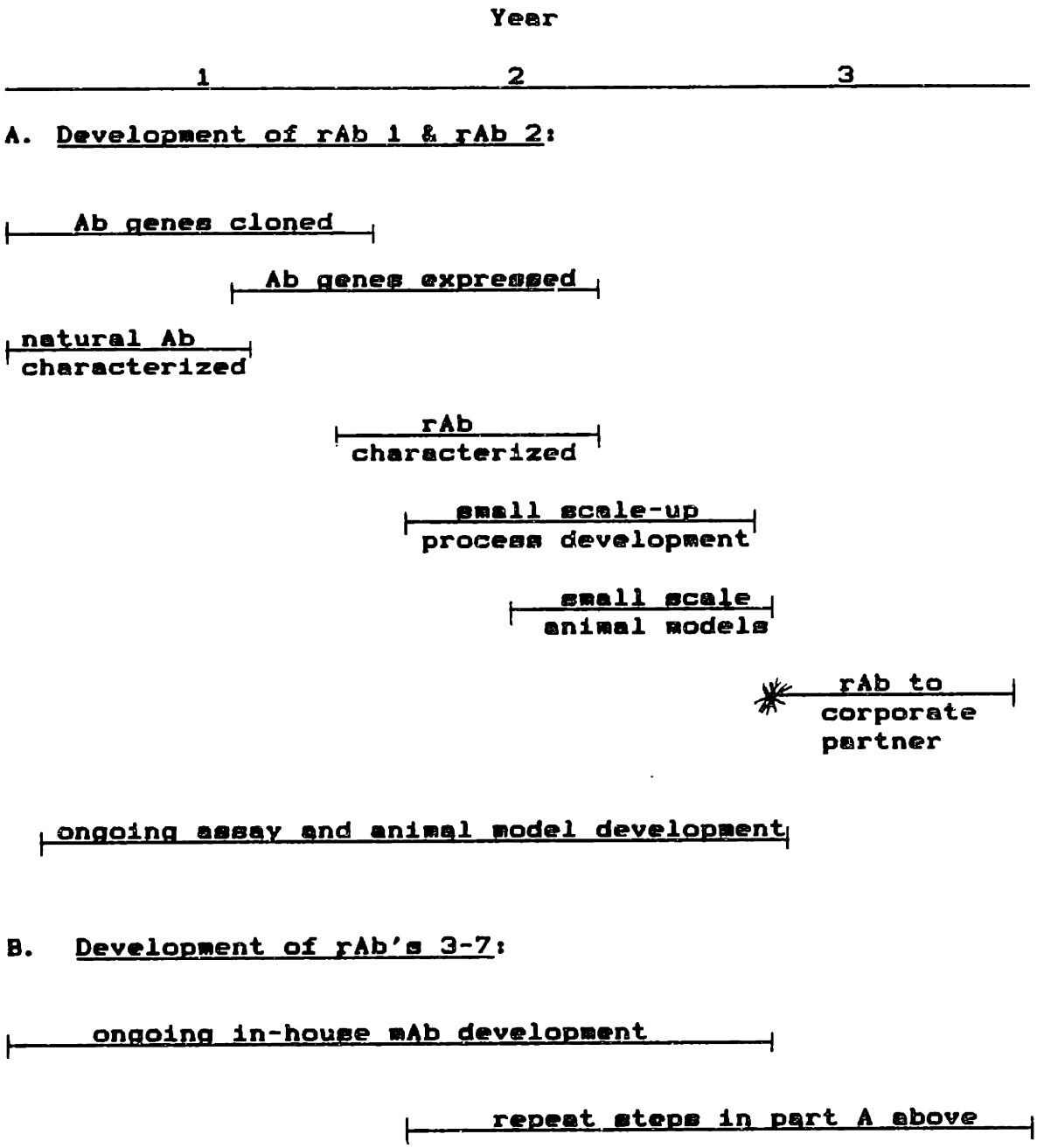


Table 20 Drug Development To Be Done By Joint Venture Partner or Licensee

1. Process development, GMP.

2. Quality assurance, process documentation.

3. Manufacture, product testing, manufacture review.

4. Clinical research, and regulatory affairs

   - IND application
   - clinical trials
   - submit NDA
   - FDA approval

5. Marketing and Sales for pharmaceutical use.

Table 21

Overall Project Goals

Recombinant Antibody (rAb) Therapeutics/Prophylactics

1. Develop rAb's and determine their efficacy in humans. Determine the efficacy of rAB's alone and/or in combination with other chemotherapeutic agents (antibiotics).

2. Obtain fast-track regulatory status for an IND review by the FDA; Begin clinical trials by the 4th quarter in year three; Conduct an aggressive, targeted phase I/II/III clinical program leading to NDA approval in year seven.

3. Develop an economic manufacturing process (either in joint venture or in-house) capable of greater than 80% gross margin.

4. Develop an internationally coordinated strategy, through joint ventures, to conserve resources and accelerate pre-clinical and clinical efforts.

5. Pursue single and combination use of rAb in parallel in pre-clinical and clinical studies.

VIII.C. Overall Project Goals

Table 21 shows the overall project goals for therapeutic and prophylactic projects. Year one, maintain current research support of rAb projects one and two (products one and two) and mAB project one (product three). Year two, provide additional support for mAb and rAb projects in terms of:

- cloning and expressing rAb's
- cell culture research
- initial *in vitro* and animal model drug testing
- understanding use of products *in vivo*.
- gather data with which to make decisions on each existing product whether to sell, drop or move into product development.

VIII.D. Functions of the Business and Research Division

The following represents both short and long term functions or goals of both business and research divisions of the Company:

1. Support the development of current and new products:
   a) clone, express and purify the product.
   b) conduct process engineering.
   c) conduct second generation process engineering.
   d) maintain ability to commit adequate resources to an acute need.
   e) support joint ventures.

2. Understand our products:
   a) characterize physically, and chemically.
   b) determine product mechanism of action at molecular and cellular (in-house); physiologic and pharmacologic levels (joint venture).
   c) discover new functions and uses.

3. Maintain quality technology in all relevant disciplines:
   a) select, train and motivate in-house scientists
   b) provide state-of-the-art knowledge and necessary equipment.
   c) recognize and acquire useful technologies outside our in-house interests and experiences.

4. Maintain team of highly motivated, creative and productive scientists:
   a) maintain heterogeneity of style, approach and skills.
   b) encourage individuals to be creative.
   c) reward each individual by title, autonomy, and material means to demonstrate their importance to the Company.
   d) encourage quality scientific publications, and both intra- and extra-mural collaborations.

5. Identify new product possibilities:
   a) via windows on outside discoveries (academia, industrial meetings).
   b) attraction of new products ideas from outside, via in-house productivity.
   c) understand consumer, physician, societal needs and wants.

6. Evaluate selected new product ideas:
   a) purify, assay and testing of new molecules.
   b) clone, express and test recombinant homologs and analogs.
   c) conduct feasibility studies.
   d) recognize and study potential products outside the in-house established interests.

7. Develop new research concepts and techniques:
   a) encourage follow through on "extraneous ideas".
   b) be open to new ideas.

IX. Financial Analysis

IX.A. Costs

An itemized list, with the dollar values, for the capital equipment requirements in years one and two are outlined in Table 22, and are $151,000 and $129,800, respectively. As the Company grows it might require further capital equipment. Therefore, an amount of $50,000/year has been set aside.

Labor costs (salaries) (Table 23) include a built in 10% increase per year. This includes an inflation and salary (promotion) increase factor. The starting salary for a Ph.D., senior scientist will be $50,000/year, and that for a B.S./M.S. scientist will be $35,000/year. Glass preparation employees will be salaried at $15,000/year and secretaries at $25,000/year.

Non-capital equipment, i.e., reagents, lab and office supplies, etc., are budgeted for $18,000/year per employee (Ph.D., B.S., M.S. scientists) and $10,000 per employee (non-scientist). This figure covers the operating costs of doing research, and general and administrative expenses (Table 24). The equipment costs (capital and non-capital) include a 5% inflation rate/year. The first year non-capital equipment costs have a built in extra $ 50,000 for the initial start-up. The Company expects to have leasing costs for the lab and office space, at $14.00/sq ft, assuming a 12 year lease.

Table 22 Capital Equipment

Capital Equipment	Year 1	2	3-12
	(Dollars)		
Sorvall centrifuge (2)	$15,000	15,000	
ultracentrifuge (1)		20,000	
Eppendorf centrifuge (6)	2,800(3)	2,800(3)	
rotors	20,000	35,000	
centrifuge adaptors	1,000	1,000	
refrigerators (8)	1,500(4)	1,500(4)	
freezers (6)	1,000	1,000	
microscopes (2)	6,000		
incubator, non-CO2 (2)	1,000	1,000	
incubator, shaking, non-CO2	3,000		
incubator, double, CO2 (3)	10,000	5,000	
water still	2,000		
water baths, constant temp.	6,000	4,000	
-70 degree freezer	5,000		
lyophillizer	3,000		
spectrophotometer	1,000		
spectrophotometer liquid scintillation counter	8,000		
	30,000		
darkroom	2,000		
balances	2,000		
pH meter	1,500	1,500	
transilluminators	1,500		
power supplies	4,000	2,000	
liquid nitrogen tank	1,000	1,000	
computer IBM PC/AT	10,000	8,000	
DNA software	2,000	2,000	
fraction collector	6,300		
vacuum pump	1,000	1,000	
stirrers/shakers	2,500		
microscope, fluorescent		20,000	
miscellaneous			50,000
Total	$151,000	129,800	50,000

note: 1. numbers in parentheses refer to the number of each item that will be purchased.
2. capital equipment refers to items with a cost greater than or equal to $1000.

Table 23 **Employee Salary Schedule**

Year
(dollars, in 1000's)

Salaries	1	2	3	4	5	6	7	8	9	10	11	12
Officers	190	209	230	253	278	306	337	370	407	448	493	542
Senior Scientists	200	220	242	266	293	322	354	390	428	471	518	570
Scientists	175	402	520	571	628	691	761	837	920	1012	1113	1224
Support	15	31	35	38	42	46	50	56	61	67	74	81
Administ.	25	53	58	64	70	77	84	93	102	112	123	135
Total Employee Salaries	605	915	1085	1192	1311	1442	1586	1745	1919	2111	2322	2554
Total Employees (number)	16	24	26	26	26	26	26	26	26	26	26	26

Note: see text for explanation.

Table 24

	Costs											
	Year											
	1	2	3	4	5	6	7	8	9	10	11	12
	(numbers in $1000's)											
1. capital equipment	151	137	55	58	61	64	67	70	74	76	81	80
2. non-capital equipment and expenses												
a. scientists	208	337	397	417	438	460	483	507	532	559	587	616
b. non-scientists	42	77	81	85	89	94	98	103	108	114	120	126
c. total (a+c)	313	414	478	502	527	554	581	610	640	673	707	742
3. salaries	605	915	1085	1192	1311	1442	1586	1745	1919	2111	2322	2554
4. lease	134	84	84	84	84	84	84	84	84	84	84	84
5. totals (1-4)	1203	1550	1702	1836	1983	2144	2318	2509	2717	2946	3194	3466

notes:

1. Capital equipment figures were taken from table 13. The numbers include a 5% inflation rate.
2. The non-capital equipment represents equipment that costs less than $1,000/item. It also includes inventory, supplies and miscellaneous items necessary for conducting R&D. The numbers are estimated at $18,000/year/employee (scientists) and $10,000/year/employee (non-scientist). It includes an extra $50,000 start-up cost and all numbers reflect 5%/year inflation.
3. Salaries were taken from table 14.

IX.B. Gross Margins

The gross margins in the pharmaceutical industry are typically high, about 80%. Therefore the Company, licensee or joint venture partner should look towards developing an economic process for manufacturing yielding 80% gross margins.

At the current price set for the Company's therapeutic products, $1000/gram, the cost of goods sold would have to be $200/gram to achieve an 80% gross margin. Currently the costs of producing FDA quality antibodies is about $200-400/gram. This depends on the amount of antibody being produced from each cell, the particular cell culture system being used and the particular growth media that is used to grow the cells. The higher cost of goods sold (greater than 20%) would decrease the gross margins to 60-80%. However, increasing the efficiency with which one can produce antibodies in large scale is currently being addressed by many university and industrial labs. The costs of producing antibodies should decline in the near future.

IX.C. Pro Forma Income Statement

The Company's Pro Forma Income Statement is presented in Table 25. The Company will not be producing its own products. It will be set up to conduct contract R&D. It will derive revenues from advance payments on royalties as a result of licensing or joint venture agreements with other companies. Depending on the exact nature of the contractual R&D arrrangement, the company could operate with a positive cash flow beginning in year two.

Table 25 **Pro Forma Income Statement**

Year
(numbers in millions)

	1	2	3	4	5	6	7	8	9	10	11	12
Revenues:												
1. Contract R&D	0.0	2.0	2.0	2.0	3.0	3.0	--	--	--	--	--	--
2. Royalties From Product Sales	--	--	--	--	--	--	3.29	8.9	14.74	61.98	100.73	164.22
Expenses:												
3. R&D	0.95	1.21	1.33	1.43	1.55	1.67	1.80	1.94	2.10	2.27	2.46	2.66
4. G&A	0.26	0.34	0.37	0.40	0.44	0.48	0.52	0.57	0.62	0.67	0.74	0.80
5. Royalties							0.66	1.42	3.88	8.52	12.30	19.96
Total Expenses	1.21	1.55	1.70	1.83	1.99	2.15	2.71	3.93	6.60	11.46	15.50	20.42
Profit Before Taxes	(1.21)	0.45	0.30	0.17	1.01	0.85	0.58	4.97	8.14	50.52	85.23	143.80

Legend to Table 25

1&2. Revenues: represents advance payments on royalties, under contract. The Company will receive 10% royalties on product sales from the joint venture partner or licensee. The numbers are obtained from projected market share data (Table 11g). The amount of advance payments in years two to six will be deducted from royalties received in year nine.

3. R&D expenses: includes all scientists salaries, capital equipment, and non-capital equipment (see Tables 22,23,24). Salaries are grossed up by 10%/yr and other figures are adjusted for 5% inflation/yr. Non-capital equipment includes $18,000/yr for working capital. The leases are expensed here. In year one, R&D expenses of $.95 million are derived from adding senior scientists salaries (.2 million), scientists salaries (.175 million), support staff (.015 million), capital equipment (.151 million), non-capital equipment and expenses (.208 million) and leases (.134 million).

4. G&A expenses: includes salaries of officers and non scientific staff (administration). Includes $10,000/yr/employee for working capital. The figures also include legal and accounting expenses. The calculation of G&A expenses are derived from adding officers salaries, administrative salaries and non-capital equipment and expenses for non-scientists in each year.

5. Royalties payments: reflect 2% royalties on sales to be paid to universities. These payments are for licensing of monoclonal antibodies necessary for the Company's first two recombinant antibody products.

In lieu of a balance sheet, Tables 22-24 contain a list of the Company's total assets.

IX.D. Pro Forma Cash Flow Analysis

Table 26 highlights the cash flows for the Company's projects for 12 years. The projects in total have a net present value of $105 million.

IX.E. Sensitivity Analysis

The Company will become profitable in year two if it successfully obtains a research contract from a joint venture partner. The before tax operating cash flows show a positive net present value (discount rate = 12%) of $105 million for the predicted 12 years in operation. This is based on all the assumptions in the business plan.

The revenues to the Company are based on 10% royalties from product sales. The revenues from product sales are based upon a $100/100mg dose per patient (therapeutic) and $20/25mg dose per patient (prophylactic). The prices are conservative and could be, realistically, 4-50 times higher. This is due to the fact that in many cases the drug will be addressing a situation where the result is life or death and/or a situation where current therapy is ineffective. This would significantly increase the royalty payments to the Company.

The dose required for treatment is estimated to be 100 mg/patient (therapeutic). If this value either increases or decreases it would reflect in either lower or higher gross margins. This in turn could affect the Company's royalty payments.

Table 26 — Pro Forma Cash Flow Analysis

	Year (numbers in millions)											
	1	2	3	4	5	6	7	8	9	10	11	12
Cash Provided by Operations:												
Contract R&D	0.0	2.0	2.0	2.0	3.0	3.0	--	--	--	--	--	--
Royalties From Product Sales	--	--	--	--	--	--	3.29	8.9	14.74	61.98	100.73	164.22
Total Cash Provided by Operations:	0.0	2.0	2.0	2.0	3.0	3.0	3.29	8		61.98	100.73	164.22
Uses of Cash:												
Increases in Capital Equipment	.151	.137	.055	.058	.061	.064	.067	.070	.074	.076	.081	.084
Increases in Inventory and Non-Capital Equipment	.250	.414	.478	.502	.527	.554	.581	.610	.640	.673	.707	.742
Total Uses of Cash:	.401	.551	.533	.560	.588	.618	.648	.681	.714	.749	.788	.822
Increase (Decrease) in Cash:	(.401)	1.45	1.45	1.44	2.41	2.38	2.64	8.22	14.03	61.23	99.94	163.40

NPV @ 12% = + $ 105.00 million

The cost of contract manufacturing, to provide FDA quality rAb's, is currently about $1000/gram. This would not be acceptible unless the Company's products could be sold for at least $5000/gram. The prophylactic units required per year and marketshares (Table 11f) are very conservative estimates. If the proper mAb's are discovered that would interact with all immunotypes of a particular bacterial strain, then the use and market share would increase significantly. This could have a significant increase in product sales and the Company's royalties.

IX.F. Proposed Offering

The Company is looking to initially raise $1,160,000.00 (Table 25, total expenses) to fund the start-up of R&D on its first and second recombinant antibody projects. It will derive the necessary funding for years two to six from advance payments on royalties from product sales. If it is unsuccessful in entering into a contractual agreement with a development partner the monies required will be $9,220,000 over five years. Yearly requirements are as follows:

Year 2: 1,550,000
3: 1,700,000
4: 1,830,000
5: 1,990,000
5: 2,150,000

These figures were determined from the total yearly expenses as listed in Table 25.

The Company could seek its funding from venture capital firms or alternatively by organizing a research and development partnership. The particular tax implications would have to be addressed at the time of offering, but would presumably offer the investors special tax benefits. The R&D partnership would be formed with the Company as the general partner and the investors serving as the limited partners. Since the partnership would own any patents, "know-how" or any intellectual property derived from the research, the Company would retain the exclusive option to purchase the partnership for a determined time period and price. The price would be pre-determined and would yield a pre tax return of some pre-determined return to the investors. Payment to the investors could be in the form of stock or royalties at their discretion. If the Company did not opt to purchase the partnership, then the investors would be free to license or sell the products or technology.

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