Biopharmaceuticals
Protection, Cure and the Real Winner

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ABSTRACT

Conventionally, product development and manufacturing of pharmaceuticals are based on small molecules and simple chemical processes. Then at the end of the genomic era, the industry was forced to adopt sophisticated biotech-based approaches for innovation of new kinds of pharmaceutical products, termed biopharmaceuticals. Following the industrial transformation, anti-cancer therapy, therapeutic proteins, vaccines and hormone therapy become the major outputs. Specific biopharmaceutical products include insulin for diabetes, erythropoietin (EPO) to treat neutropenia, granulocytes-colony stimulating factors (G-CSFs), growth hormones, and cytokines (for therapeutic purposes). Currently, monoclonal antibodies (mAbs) are the fastest growing therapeutic proteins in R&D and market globally; targeting at cancer treatment, inflammatory and immune related diseases. Existing cytotoxic drugs have been rejuvenated via conjugation technology with MAbs to improve effects of the former. Lead by mAbs, therapeutic protein market has claimed at least 30% of the total value of biopharmaceuticals in the global market. Cytokines is already in advanced development for treatments of cancers, benign prostatic hyperplasia, gout and inflammatory conditions. Interestingly, insulin has been in the market for a long time, but R&D efforts are still strong especially on new formulation and delivery of oral or other non-invasive dosage. On the other hand, even though many vaccines are already well established in the market, new technologies are still needed to make those vaccines become more potent, cost effective and convenient. Previously, it was almost impossible to accelerate development of vaccines against some diseases as it was limited by technology. Currently, there are many new vaccines against existing targets and vaccines against new targets in the pipeline. Despite numbers of failures in the past, many biopharmaceutical companies

are not discouraged to develop difficult vaccines against major problems or complex diseases including malaria, dengue, hepatitis C and HIV. Acute issues on diseases, for instance bio-terrorism, SARS and influenza, became a major growth driver for development of new vaccines and method of production. The cost of producing biopharmaceuticals is nowhere going to be cheap. The advancement of biopharmaceutical industry also stimulates "fringe industries" that supports the entire value chain, for example an improved bio-process technology, chromatography, bio-assay development, preclinical and clinical trials contract research organisation (CRO), sophisticated manufacturing technology, bioinformatics, contract manufacturing organisation (CMO), cold-chain management and logistics. From the business perspective, the requirement for highly specialised knowledge and skilled worker, great amount of funding required for investment and long-term investment horizon with a big loop in J-Curve serve as great barriers to new entrants. Despite the high risks, many sophisticated investors treated this as a great opportunity for potential higher returns from successful investee companies, provided that they are well equipped with the necessary bullets for evaluation, forecasting and making the right decision before joining the party.

INTRODUCTION

The information needed to synthesize proteins, enzymes and ensure 'normal' working of the body is coded by the genome. The genome is the complete genetic make-up of an individual and, in human, it is made of double helical strands of DNA. Specific sequences/ arrangements of the DNA, known as genes, contain information for synthesizing all the proteins and enzymes present in the body. The DNA strand consists of a chain of interlinked nucleotides, which are made of deoxyribose (a sugar) a phosphate group and an organic base, and hence the name deoxyribonucleic acid. Only four different bases - adenine (A), thymine (T), cytosine (C) and guanine (G) – are present in human/animal body. The base is attached to the sugar of a sugar-phosphate-sugar-phosphate structure and forms a strand. Complementary pairing of A-T and G-C of adjacent strands by hydrogen bonding results in the double helical DNA, similar to a twisted ladder. Aberrations in the sequence due to deletions, insertions, rearrangements and mutations are responsible for causing diseases. With the completion of Human Genome Project, 99.9% of the gene rich portion of the human genome has been sequenced. Currently, genomes of several animals, plant and microbes have been sequenced and, now, it could be accomplished at an affordable cost. In Malaysia, there are at least two government research institutions and one public listed company have acquired the capability to complement the genome sequencing services to the public.

Protein synthesis begins with unwinding of the DNA double helix. The free strand of DNA then binds to 'free' bases present within the nucleus. The complementary strand created is known as messenger RNA (mRNA), and this process is known as transcription. During transcription, non-coding regions and other exons are removed. The transcribed mRNA enters the cytoplasm

and attaches to ribosomes. Each triplet of bases on the mRNA is known as a codon and codes for a specific amino acid. Triplets of bases on the transfer RNAs (tRNA) that are complementary to codons are known as anti-codons. Each anticodon binds to a particular amino acid present in the cytoplasm. The anti-codons on tRNA along with amino acids attach to complementary codons on mRNA and this process is known as translation. The sequential arrangement of amino acids as anti-codons bind to codons results in synthesis of proteins, by adding amino acids one by one akin to adding beads on a string.

A variation in the sequence of bases, termed as single nucleotide polymorphisms (SNPs), might be responsible for diseases. The altered sequence could code for defective proteins or enzymes, leading to disease manifestation. The most common variation is a single base substitution, known as single nucleotide polymorphism. Other serious defects are caused by mutations, which could range from deletion of a segment to translocation of chromosomal material to genetic inversions. Matters only worsened with multigenetic diseases such as cancer, diabetes, and heart disease, as no one had a clue as to what genes or interactions of sets of genes were responsible for these ailments. Improvement in sequencing technology raised hopes that answers might be just around the corner. The identity of defective region in our genome could give an insight into the disease pathogenesis and could also help identify novel drug targets.

Drug discovery and development has been likened to trial-and-error, involving screening for drug candidates amongst millions of compounds. It has been estimated that for every 5,000 potential candidates initially identified, 5 will enter clinical trials and ultimately one will be approved. The cost of developing one drug is staggering and now estimated to be RM2.5billion (USD800million)

instead RM1.6billion (USD500m) 10 years ago, with 42% being spent on preclinical studies and the remainder on clinical studies. Of all the drugs that are ultimately launched, about 10% of them face withdrawal due to some serious adverse reactions in patients. Avoiding these kinds of fiascos, either in late stage clinical trials or post-launch, could result in huge savings for the companies involved. Another source of savings to drug developers could come from reducing preclinical drug candidates to a more manageable level. In order to realise this, ones must understand the underlying genetic factors of the disease target. This approach suggests a departure from the trial-and-error approach to a more systematic approach where defined genetic areas will be targeted. Then, number of available genetic targets will determine the number of candidate drugs entering preclinical studies. As the number of candidate drugs entering the pipeline reduced, apart from increased productivity, investors and biopharmaceutical R&D companies will benefit from a cost perspective. An example of the kind of impact that genomic studies could have is the change of label for Pfizer's Irinotecan in 2005. Approved in 1996, Irinotecan is used to treat lung and colon cancers. In another example, dentification of the Her2 gene leads to the development of Herceptin. About 20% of breast cancer patients are classified as Her2 subtype, and Herceptin caused a 33% increase in longevity in such patients. Similarly, 10% of lung cancer patients have activation of Epidermal Growth Factor (EGF) and administering Iressa increased average life expectation from one to two years, a 100% increase. However, this claim is debatable as a study failed to show any survival benefit.

At a glance, development and commercialization of biopharmaceuticals appears to be straightforward as the biology of endogenous compounds, clinical and safety profile often are well known. However, given by tremendous recent advances in

genetic understanding, biotechnology and knowledge of protein function, an explosion of novel opportunities for development of biopharmaceuticals is definitely a great opportunity to the many. The complexity of pharmaceutical development, manufacturing process, competitive landscape, funding, commercialization issues, and meeting regulatory requirement are of a tremendous challenge in the development of novel biopharmaceuticals, to bring them to the market and finally to the ensure real benefits reach the patients.

MONOCLONAL ANTIBODIES, THERAPEUTIC PROTEINS & VACCINES

Post genomic era has been accomplished by many new inventions. Despite the few blockbusters success many products or associated-corporate failures were unknown to general public. Products manufactured by using of biotechnology methods, intended for pharmaceutical purposes, have been commonly referred as "biopharmaceuticals" or "biodrugs". Biopharmaceuticals are closely related with biological sources usually involving live organisms or their active components. Biopharmaceuticals include monoclonal antibodies, proteins produced by recombinant or cell culture technologies, vaccines, blood or plasma derivatives, and cell/tissue culture have changed the pharmaceutical landscape tremendously. The methods used in identification, development, production, and delivery of biopharmaceuticals differ often from methods used in traditional pharmacology (Lievonen, 1999). Currently, many biopharmaceutical products have been well received by target market and dominated mainly by monoclonal antibodies (MAbs), therapeutic proteins and vaccines.

Monoclonal Antibodies (MAbs)

In contrast to polyclonal antibodies, MAbs are known to specifically recognise and bind to a single type of antigen. They are typically made by fusing myeloma cells with the spleen cells from a mouse or B-cells of rabbits that has been immunized with the desired antigen. The antibody molecules contain 2 heavy-chains and 2 light-chains. There are several various types of MAbs: 1) Murine: A murine antibody is one in which both chain types are of mouse origin; 2) Rat: Both chain types are of rat origin; 3) Chimeric: In a chimeric antibody both chain types are chimeric as a result of antibody engineering. A chimeric chain contains a foreign variable domain (V-D-J REGION) (originating from one species other than human, or synthetic) linked to a constant region (C-REGION) of human origin; 4) Humanized: A humanized antibody is one in which both chain types are humanized as a result of antibody engineering. The complementary determining regions (CDR) of the variable domains are foreign (originating from one species other than human, or synthetic) whereas the remaining chain is of human origin; 5) Human: In a human antibody both chain types, and the J chain in the case of polymeric antibodies, are of human origin.

Current estimated value of the global MAb market is more than $38bn represented by ophthalmic (24%), anti-viral (8%), anti-cancer (32%) and anti-TNF (26%). Currently in the pipeline are antibody therapies for almost every form of cancer. Monoclonal antibodies have been used to treat cancer for the past decade and are one of the most promising treatment options presently available. As new cancer-associated antigens are discovered, scientists are developing antibodies to target them. The use of antibodies to treat cancers is preferred for three main reasons: 1) many view antibody treatment as a form of ‘passive immunotherapy’ because the cells are made in the laboratory rather than in the patient’s body; 2) As

opposed to traditional chemotherapy, which is non-specific and can therefore result in debilitating side effects, antibody treatments can be targeted directly to the affected cells, thereby reducing the side-effects; and 3) most important, they have been shown to work experimentally, clinically and acceptable post-marketing feedback.

There are two forms of MAbs preparation: *naked MAbs* and *conjugated MAbs*. The later is prepared by joining suitable MAbs to a well known chemotherapy drug, radioisotope or toxin.

Naked MAbs

Naked MAbs are the most commonly used and in cancer treatment. They often attach to malignant cells, acting as a marker so that the body's immune system can recognize and destroy them. Examples: 1) *Rituxan* (rituximab by Biogen-Idec/Roche/Genentech/Chugai) - a murine/human chimeric antibody that targets CD20, a protein that is present on more than 90% of B-cell lymphomas. It is primarily indicated for the treatment of non-Hodgkin's lymphoma (NHL) and for a number of specific indications within this overall diagnosis; 2) *Campath* (alemtuzumab by Genzyme/Bayer) is a recombinant DNA-derived humanized MAb that is directed against the cell surface glycoprotein CD52, which is expressed on the surface of normal and malignant B and T lymphocytes, NK cells, monocytes, macrophages and tissues of the male reproductive system. It is currently indicated for the treatment of refractory B-cell chronic lymphocytic lymphoma (CLL); 3) *Herceptin* (trastuzumab by Genentech) is a chimeric humanized mAb indicated for the treatment of breast cancers over-expressing the HER2/neu protein, which is present in large numbers on tumor cells, including certain breast cancers. When this protein is activated, it helps the cancer cells to grow. Trastuzumab stops the protein from becoming active. HER2 over-expression is found in around 25% of primary breast

cancers, possibly higher in metastatic cases. HER2 over-expression is generally associated with lower responsiveness to cytotoxic chemotherapy. Herceptin was approved for the treatment of HER2+ metastatic breast cancer (as either a monotherapy for chemotherapy-failure patients or in combination with paclitaxel as a first line therapy) in 1998; 4) *Erbitux*: (developed by ImClone) is a human-murine chimeric IgG1mAb targeted against EGFR, a receptor expressed on cell surfaces in many tumor types which is implicated in the development of resistance to the effects of chemotherapy. Like HER2/neu, EGFR is found on some tumor cells and helps them grow and divide. Erbitux was approved for use in combination with Camptosar (irinotecan, Pfizer) for Camptosar-refractory colorectal cancer patients or as monotherapy for recurrent metastatic colorectal cancer in patients intolerant to Camptosar. Erbitux was approved for some advanced colorectal cancers and for some head and neck cancers; 5) *Avastin* (bevacizumab, Genentech) is a humanized IgG1 monoclonal antibody targeting vascular endothelial growth factor (VEGF), a protein normally made by tumor cells to attract new blood vessels and facilitate growth of the tumor. Bevacizumab attaches to VEGF, thereby blocking it from signaling for new blood vessels to form. It helps stop new blood vessel formation in tumors and it also may improve drug delivery so that chemotherapy can kill more effectively. Avastin was the first anti-angiogenesis drug approved for cancer treatment, and is usually combined with cancer-killing chemotherapy. It was approved in 2004 to treat colorectal cancer, and for non-small cell lung cancer in 2006. Even without approval for wet age-related macular degeneration, many doctors use it for this purpose instead of the more expensive drug Lucentis (ranibizumab, Genentech).

Conjugated MAbs

Conjugated MAbs are used to carry chemotherapy drugs, radioisotopes or toxins specifically direct to target cancer cells. The approach shall reduce the potential casualties or damages to non-target cells. With such high specificity brought to target cells, the desired effects shall be much more intense than naked MAbs but the same is applicable to the potential side-effects. Conjugated MAbs are grouped into radiolabeled, chemolabelled, and immunotoxins: 1) *Radiolabeled antibodies*: *Zevalin* (Yttrium-90-labeled Ibritumomab tiuxetan, CTI Seattle) consists of an anti-CD20 murine-derived MAb coupled with a primarily beta-radiation emitting isotope, which allows for imaging of the patient and localization of the radioimmunoconjugate. The result is a dual action product that binds to the target antigen CD20, found on B-cells, initiating an immune response against the B-cell non-Hodgkin's lymphoma and concurrently delivering a dose of radiation directly to tumor cells. Other examples are Bexxar *(Iodine-131-labeled tositumomab, GlaxoSmithKline)*, like Zevalin, consists of an anti-CD20 murine-derived MAb coupled with a primarily beta-radiation emitting isotope, and it is for treatment of certain types of non- Hodgkin's lymphoma that no longer respond to rituximab or chemotherapy; and *ProstaScint (Cytogen) a* monoclonal antibody tagged with Indium-111, used to locate prostate cancer. Then a gamma camera detects the radiation given off by the radioisotope; 2) *Chemolabelled antibodies:* Several chemolabelled antibodies are currently in clinical trials but none is approved for use; 3) *Immunotoxins*: *Mylotarg* (gemtuzumab ozogamicin, Wyeth) is another humanized anti-CD33 IgG4 conjugated to calicheamicin, a potently cytotoxic natural product that induces double-stranded breaks in DNA. The CD33 antigen is present on most leukemia cells. Gemtuzumab is the

only immunotoxin to date approved by the FDA for the treatment of cancer.

Market status of MAbs

Since 1988, beginning with Orthoclone (Muromonab-CD3 by Jansenn-Cilag; murine MAb to suppress rejection of transplants), approximately 30 MAbs for therapeutic applications are already in the market worldwide. Despite reaching the maturity in the market, the degree of importance and demand is increased due to the specificity of the application intended for target diseases. Currently, the value of MAb market globally *in circa* RM121 billion and expected to overtake pharmaceuticals in the near future.

Table 1 MAbs products , pre-marketing 2010

Generic	Trade name	Indication	Company
catumaxoMAb	Removab	Cancer	TRION/Fresenius
ofatumuMAb	Arzerra	Cancer	GSK
efunguMAb	Mycograb	Infection	Novartis
denosuMAb	Prolia (onco)	Cancer	Amgen
motavizuMAb	Numax	Infection	AstraZeneca
Canakinmuab	Ilaris	Inflammation	Novartis
nimotuzuMAb	Theraloc	Cancer	Oncoscience

Therapeutic Proteins

Erythropoietin (EPO)

Erythropoietin (EPO) is a glycoprotein hormone that regulates erythropoiesis (production of red blood cells). It produced naturally by kidney. As cytokine, it acts on erythrocyte precursors. EPO is

important in the brain's response to neuronal injury and in the wound healing process. The recombinant erythropoietin (RhEpo) is indicated for treating anaemia patients i.e., for patients with kidney disease who are on dialysis; treatment of anaemia who are with chronic kidney disease but not on dialysis. Logically, since EPO accelerated erythrocytes production it also increases oxygen carrying capacity. This fact did not escape the sight of the athletic community. It had been used illegally as a blood doping agent in endurance sport for performance enhancing and there was no direct test to distinguish natural EPO from pharmaceutical EPO until year 2000.

Growth hormone (GH)

Growth hormone (GH) is a polypeptide hormone that stimulates growth and cell reproduction in humans and other animals. It is synthesized, stored, and secreted by the somatotroph cells in the anterior pituitary gland. Somatotrophin refers to the native growth hormone, while the term somatropin refers to GH produced by recombinant DNA technology, and is abbreviated "rhGH". GH has a variety of functions in the body, the most noticeable of which is the increase of height throughout childhood. In children, growth failure and short stature are the main results of GH deficiency. Common causes include genetic conditions and congenital malformations. Deficiency can also cause delayed sexual maturity. In adults, deficiency is rare, the most common cause being pituitary adenoma.

In human, rhGH is used as replacement therapy in adults with GH deficiency of either childhood-onset) or adult-onset. In these patients, benefits are varies to include reduced fat mass, increased lean mass, increased bone density, improved lipid profile, reduced cardiovascular risk factors, and improved psychosocial well-being. rhGH has also been used to treat conditions which produce short

stature which are not related to deficiencies in GH, though results are not as dramatic when compared to short stature solely due to deficiency. Examples of other causes of shortness often treated with GH are Turner syndrome, chronic renal failure, intrauterine growth retardation, and severe idiopathic short stature. Some doctors have started to prescribe growth hormone in GH-deficient older patients (but not on healthy people) to increase vitality. While legal, the efficacy and safety of this use for human growth hormone (HGH) has not been tested in a clinical trial. HGH has been used by competitors in sports since the 1970s, and it has been banned by the relevant authorities.

The use of GH has also been studied in raising livestock and several efforts have been made to obtain governmental approval to use GH in livestock production. These uses have been controversial. In the United States, the only FDA-approved use of GH, is the use of a cow-specific form of GH called bovine somatotropin for increasing milk production in dairy cows.

Genentech (USA) pioneered the first use of recombinant human growth hormone for human therapy in 1981. Prior to this, growth hormone used to treat deficiencies was extracted from the pituitary glands of cadavers. Attempts to create a wholly synthetic HGH failed. Limited supplies of HGH resulted in the restriction of HGH therapy to the treatment of idiopathic short stature. In 1985, biosynthetic human growth hormone replaced pituitary-derived human growth hormone for therapeutic use.

Table 2 Human growth hormone products in the market for treating GH deficiency

Company	Generic	Product
Pfizer	RhuGH	Genotropin
Novo Nordisk	RhuGH	Norditropin
Eli Lilly	RhuGH	Humatrope
Genentech	RhuGH	Nutropin, Protropin, Somatropin, Somatrem
Ipsen	RhuGH	Nutropin AQ pen, Somatropin
Merck Serono	RhuGH	Saizen/Serostim

Cytokines

Cytokines are signaling proteins and glycoproteins that are used extensively as intermediate for inter-cellular communication. They are produced by a wide variety of heamatopoietic and non-haematopoietic cell types and their effects are sometimes strongly dependent on the presence of other chemicals. Cytokines are critical to the development and functioning of both the innate and adaptive immune response. Since cytokines are involved in various activities of the immune system, they are considered to be immunomodulators. The cytokine family consists mainly of smaller, water-soluble proteins and glycoproteins. Cytokines are critical to the development and functioning of both the innate and adaptive immune response. Cytokines are classified by structure; members of the largest group of cytokines are divided into three sub-families: 1) Interleukin-2 (IL-2) subfamily; 2) Interferon (IFN) subfamily; and 3) Interleukin-10 (IL-10) subfamily. The first of these three subfamilies contains several non-immunological

cytokines including erythropoietin (EPO) and thrombopoietin (THPO). Since cytokines are involved in immune system activity, they are considered as immunomodulators from the therapeutic point of view. Novel cytokine-based therapies focusing on different immunomodulatory targets have been, and are being, developed. Many of these emerging strategies either target, or consist of, interleukin molecules. However, no single interleukin has emerged as the one to target for modulating the immune system. Instead, companies are targeting a number of different ILs as well as other cytokines. The market opportunity for specific agents in development will depend on the indication(s) for which they receive approval. Many of these compounds are being evaluated for the treatment of debilitating conditions such as asthma, cancer, and certain autoimmune diseases. If they can demonstrate improved efficacy and/or safety compared to current therapies, many of these novel immunomodulators have the potential to achieve blockbuster status.

Table 3 Cytokines in development

Company	**Target Cyotokine**	**Clinical trial**
Cel-Sci	Natural human IL-2 and other cytokines	Phase III
Neopharm	Recombinant protein consisting of IL-13 and cytotoxic agent PE38	Phase III
Protox	IL-4 combined with Pseudomonas exotoxin	Phase II
Regeneron	IL-1 Trap Designed to bind to IL-1 and neutralize it	Phase III
Renovo	Recombinant IL-10	Phase II

cont. Table 3

Synta	Oral IL-12/IL-23 inhibitor	Phase II
ZymoGenetics	IL-21 IL-29 Also known as interferon lambda-1	Phase I Preclinical
Vical	Gene therapy; DNA encoding IL-2	Phase I

Insulin and Diabetes

Insulin

Insulin is the first therapeutic protein used in modern medical practice (beginning in year 1922). Bovine and porcine pancreases were the main source of insulins. Later the "humanized" form of insulin (based on pig insulin) was made by replacing pig-specific amino acid with human-specific amino acid. "Non-Halal" insulin was an issue until human insulin manufactured from cloned human insulin genes. The insulin molecule has been modified via genetic modification for various purposes to accommodate the desired pharmacokinetics. Several companies have invented insulin analogues: Eli Lilly with insulin lispro (Humalog), Novo Nordisk with insulin aspart (NovoRapid) and Sanofi-aventis with insulin glulisine (Apidra). In contrast to the original insulin, these analogues are absorbed very rapidly and the variability of their effect is minimized. For long action insulin, Sanofi-aventis produced another analogues namely insulin glargine (Lantus) and Novo Nordisk with insulin detemir (Levemir).

Type 1 diabetes

Type 1 diabetes, previously referred to as insulin-dependent diabetes mellitus occurs most commonly in children or young adults and constitutes 5–10% of the diagnosed diabetes patient population. The pancreatic islet beta-cells are destroyed by an autoimmune attack and that causes daily needs of insulin injection by all type 1 patients. Without an administration of exogenous insulin, patients enter diabetic ketoacidosis, which is a potentially life-threatening complication of type 1 diabetes. An administration of insulin injections is beset with several challenges: 1) Mode of administration – except for bucally absorbed insulin and insulin pumps, all insulin is self-administered through a subcutaneous injection. Although insulin needles are very small (29–31 gauge) and relatively painless, injections still pose a significant disadvantage for insulin therapy initiation due to patients' fear; 2) inconvenience of use – injections may need privacy for administration, unlike noninvasive treatments that can be taken anywhere; 3) weight gain and increased cardiovascular risk – a very common side effect of standard subcutaneous insulin therapy is weight gain (approximately 2–4kg or 4.4–8.8 lbs.); 4) Hypoglycemia – although injecting insulin is a fast-acting drug delivery method, patient compliance tends to be poor due to the inconvenience in their administration, thereby leading to poor glycemic control.

Type 2 diabetes

Type 2 diabetes, previously known as adult-onset diabetes, accounts for 90–95% of diagnosed diabetes cases globally and typically develops in middle-aged adults. Type 2 diabetic patients have the ability to produce insulin but have an impaired response (or insulin resistance) to the effects of insulin, which leads to high levels of blood glucose. Insulin resistance in Type 2 patients is associated

with increased calorie consumption and higher meal frequency, which chronically activates the body's insulin response. This leads to a reduced cellular sensitivity to the effects of insulin and higher insulin production to compensate and achieve a normal blood glucose level. However, the continued positive feedback loop leads to an inability of the body to produce enough insulin for maintaining a normal blood glucose level. Type 2 diabetes patients generally have normal to elevated insulin production. However, for cases where this alone is not effective, oral antidiabetics are prescribed, which are followed up with insulin therapy in cases where even oral antidiabetics are ineffective. Some of these oral drugs act by stimulating additional insulin secretion from the pancreas (known as insulin secretagogues) or sensitizing the body to the already available insulin (known as insulin sensitizers), or decreasing the production of glucose from the liver. When all of the available agents fail, as in the case of Type 1 diabetics, Type 2 patients also require exogenous insulin. The leading drug treatments available are sulfonylureas and metformin, both of which are characterized by a high level of genericization. Thiazolidinediones are insulin-sensitizing agents used in combination with other oral antidiabetics and/or insulin, although they are associated with weight gain and are also contraindicated in patients with congestive heart failure. In general the insulin dose required in type 2 patients is considerably higher than in Type 1, since the underlying insulin resistance is overcome only by a greater insulin load.

Table 4 Global diabetes market, 2007/08

	Value USD, millions	Growth (%)
Insulin market		
Human insulins	12,278	19.7
Animal insulins	16	4.7
Total: Insulins	**12,294**	**19.7**
Drugs targeting underlying causes		
Glitazone	6,217	-7.9
Sulfonylurea	2,001	2.7
Biguanide	1,954	5.9
DPP-IV	1,725	145. 5
Alpha-glucosidase inhibitor	1,057	11.9
GLP-1	700	19.8
Glinide	812	12.7
Total: drugs targeting underlying causes	**14,465**	**7.2**
Other anti-diabetics	395	16.6
Insulin devices	140	19.2
Total: diabetes market	**27,294**	**12.7**

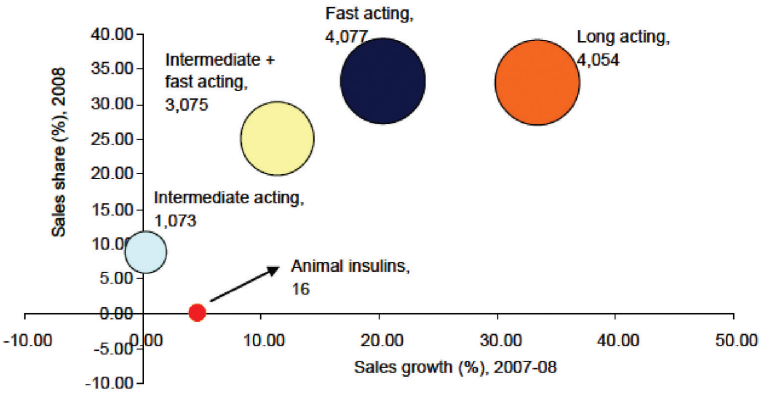

Figure 1 Relative positions of different types of insulins. Bubble size represents sales in USD $m. Sales of intermediate and long-acting insulins were 0.31m (notappearing in the figure).

Source: IMS Health, 2009

Table 5 Examples of Late-stage diabetes R&D pipeline

Brand	Company	Mechanism	Status
Alogliptin (SYR-322)	Takeda	DPP-IV	Registration
Victoza (liraglutide)	Novo Nordisk	GLP-1	Registration
Ondero (linagliptin)	Boehringer Ingelheim	DPP-IV	Phase III
taspoglutide	Roche/Ipsen	GLP-1	Phase III
AVE0010	Sanofi-Aventis	GLP-1	Phase III
Syncria (albiglutide)	GSK	GLP-1	Phase III
dapagliflozin	BMS/ AstraZeneca	SGLT-2 inhibitor	Phase III

cont. Table 5

teplizumab (MGA031)	Eli Lilly/ MacroGenics	Anti-CD3 monoclonal Antibodies	Phase III
otelixizumab	Glaxo/Tolerx	Anti-CD3 monoclonal antibodies	Phase III
Technosphere insulin	Mannkind	Inhaled Insulin	Phase III

Innovation in drug delivery mechanisms, including the use of non-invasive insulin therapy does help in making the treatment more convenient. The introduction of oral and inhaled insulin will make drug delivery more convenient and help in improving patient compliance, leading to better glycemic control. Other innovations in type 1 diabetes treatment include ongoing research in islet cell transplantation and stem cell therapy, both of which are aimed at addressing the cause of the disease. Experimentally, caprine pancreatic islets have been cultured successfully *in vitro* and optimized for potential future xenotransplantation (unpublished).

Xenotransplantation for production of insulin

There is limited availability of human donors to provide pancreatic islet cells to Type I diabetes patients. Meanwhile, the search for alternative islet sources in pancreatic islet transplantation has been extended to number of animal species such as porcine, bovine, fish, rat, mouse and monkey. Well-established xenotransplantation studies have been reported in large animal organ donors, e.g. pig and bovine. Whether caprine species could be an alternative donor for the source of pancreatic islets for diabetes researches and transplantation trials requires optimized isolation and purification

methods. Despite various influencing factors for the final yield of islets, once isolated, islets are fragile and difficult to maintain. An early study has shown that caprine pancreatic islets could be cultured with desired viability and functionality, and potentially could be used as an alternative source of islets for diabetes and transplantation researches.

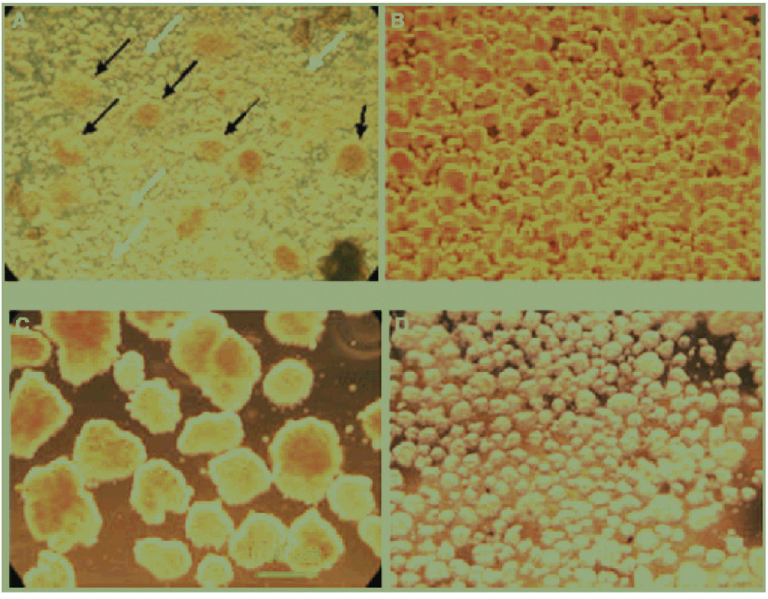

Figure 2 Dithizone (DTZ)-stained caprine pancreatic islets seen under inverted microscope are presented in crimson red in center part of clusters, where b-cells are integrated; therefore, DTZ molecule stains zinc in insulin granules and gives the islets a distinctive red color. Panel A: Recovered islets from Euro-Ficoll density gradients before optimization (black arrows). Purified islets with abundant aggregated cells and acinar tissue (white arrows) (magnification x40). Panel B: Recovered islets from optimized Euro-Ficoll density gradients. High-purity islets yield with few aggregated cells and acinar mass (magnification x40). Islets purity is estimated above 90%,while it is performed roughly by proficient observation. Panel C: Islets are presented in different sizes and shapes. Hence, the particles larger than 50 um are counted as viable and mature islets (magnification x100). Panel D: the stain's color of islets disappeared few hours after staining, washing with Hank's balance salt solution and transferred to culture media (magnification x40).

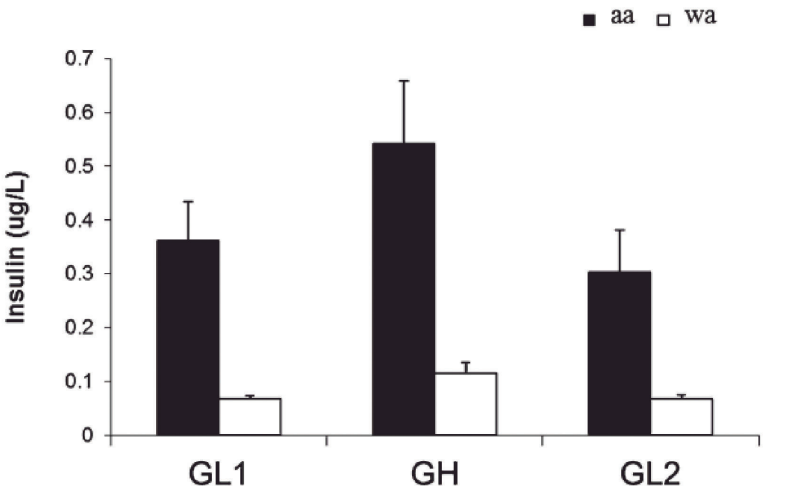

Figure 3 Insulin release in response to glucose challenge in isolated caprine islets in presence of l-glutamine and theophylline (aa) or absence of l-glutamine and theophylline (wa). The islets were exposed to 1.67 mm/l glucose (GL1) for 1 h, to 25 mm/l (GH) for a second hour, and finally to 1.67 mm/l (GL2) for a third hour. Values are means ± SE. Interaction effect between two treatments applied (different glucose concentrations vs. presence or absence of l-glutamine and theophylline) in this experiment is not significant.

Table 6 The summary of therapeutic proteins in development worldwide

Company	Technology	Status
Oramed Pharmaceuticals	Oral insulin delivery technology	Phase II
Cytheris	Critical immune-modulator for immune T-cell recovery and enhancement in HIV-1 infected patients classified as Immunological Non Responders (INR)	Phase II

cont. Table 6

Flamel	Technologies Controlled release form of unmodified interferon alpha-2b for treatment of chronic hepatitis C virus (HCV) REPLAGAL Shire Enzyme replacement therapy for Fabry BLA (agalsidase alfa) disease (galactosidase deficiency)	Phase II
Human Genome	Genetic fusion of human albumin and (albinterferon Sciences (Novartis) Interferon alfa using proprietary HGS MAA alfa-2b) albumin-fusion technology.	Phase II
Biovitrum	Recombinant Factor VIII Fc fusion (rFVIIIFc) protein for treatment of hemophilia A. rFVIIIFc is being investigated for the potential to prolong protection from bleeding and reduce frequency of injections.	Phase II
Cytheris	Second-generation rhIL-7 in combination with standard antiviral treatment and vaccination in HBeAg-negative chronic hepatitis B-infected (HBV) patients	Phase II
Teva Pharmaceutical	Biosimilar product to Neupogen containing BLA G-CSF for reduction in the duration of severe neutropenia and the incidence of febrile neutropenia in patients treated with established myelosuppressive chemotherapy for cancer.	Phase II
ERYTech Pharma	Enzyme formulation of L-asparaginase improved by entrapment and protection of the enzyme inside homologous red blood cells	Phase II

cont. Table 6

Lundbeck A/S	Novel carbamoylated form of human erythropoietin (EPO) intended for patients with Friedreich's ataxia	Phase II
Taspoglutide Ipsen/Roche	Weekly glucagon-like peptide-1 (GLP-1) analogue for diabetes	Phase III
ZymoGenetics	PEG-Interferon lambda (IL-29) is a novel type 3 interferon	Phase II

Vaccines

Many infectious diseases have been largely controlled (or being eliminated in case of smallpox) through mass use of vaccines to create "herd immunity" situation. Mass vaccination blocks the chain of an outbreak. However, some uneducated members of community worry about the potential side effects of vaccines without considering their benefits outweigh potential minimum side effects. Side effects of approved vaccines, whilst real, whether for human or animals, are either far less serious than actually catching the disease, or are very rare, and argue that the risk/benefit ratio should be based on benefit to humanity (or socio-economic benefits) rather than simply on the benefit to the immunized individual.

Despite the major success of vaccine and vaccination program, there remain many hurdles and challenges to develop new vaccines especially for common diseases including malaria, HIV and dengue. Several companies have invested more than USD200 million to develop dengue vaccine in the past 10 years but failed to bring the vaccine to the market. Often experimental vaccines elicit an immune response that does not actually protect against the disease. What is the problem? Most vaccines preferentially cause production of antibodies rather than cell-mediated immunity. This works fine for diseases caused by toxins (diphtheria, tetanus), or extracellular

bacterial (pneumococcal), or viruses that must pass through the blood circulation system to reach the tissues where they cause cellular damage (polio, rabies). However, intracellular parasites including viruses while they reside within target cells cannot be reached by antibodies. Thus our immune system will recruit immune cells e.g., cytotoxic T lymphocytes (CTLs) to attacks those infected cells. Most vaccines failed to induce good cell-mediated immunity (CMI). In case of HIV/AIDS, earlier experimental vaccines focused on the antibody response and failed. That well explained why thousands of patients dying of AIDS despite their high levels of anti-HIV-1 antibodies. Certainly, vaccines that elicit only antibody response will not protect individual from AIDS.

An alternative to conventional vaccines is DNA vaccines, one of new modes of vaccination. The technique involves with introduction of DNA molecules encoding the antigen into the body of the target patient e.g. via intra-muscular injection. DNA molecules that carrying genetic codes cause the desired antigen or protein to be produced *in vivo*. Both cellular and humoral immune systems shall response to the specific antigen, and also the immune response can be polarized either to TH1 or TH2 immune T-cells. Delivery of DNA directly to individual is also applicable for other purposes other than vaccination, including gene therapy and diagnostic purposes. DNA vaccines have several distinct advantages, which include ease of manipulation, use of a generic technology, simplicity of manufacture, and chemical and biological stability. In addition the target organ can be specifically targeted and the duration of the immune response.

Table 7 Summary of new vaccine technologies

Technology	Description
Plasmid DNA or DNA Vaccine	Vaccine induced good humoral and cellular response in animals. Mostly cellular responses seen in cancer, HIV-1, malaria. Prime-boost using pox viruses gives promising results. Vaccine delivery is by adsorption onto gold particles ("gene gun") or formulated with cationic lipids.
Cellular vaccines	Dendritic cells are obtained from patients recruited in vitro for a few weeks. These cells are primed/ exposed to target tumor lysates of tumor-associated antigens - DNA, RNA, proteins or peptides, then re-administered to patients.
Lipopeptides	Peptide antigen attached to lipid moiety of lipoprotein; T-cell response induced against HBV and HPV. Being tested against HIV-1 Viral vectors ALVAC (canarypox vaccine) already used; other pox viral vectors also tested in humans include fowl pox vaccinia and MVA (Modified Vaccinia Ankara strain).
Transgenic plants	Antigens for vaccine preparation have been successfully expressed in potatoes, tobacco, tomatoes and bananas for oral immunization of animals. Safety concerns in human is related to the risk of inducing tolerance
Vaccine delivery devices	Include patches, powered injection devices, aerosols for powdered vaccines and micro-needles for transdermal immunization.

Current vaccine market

Currently, the global human vaccine market is fairly evenly divided between pediatric and adult vaccines, each accounts for about half of the total vaccine market, valued at $18bn for 2009. In volume terms, there is far greater disparity, because most pediatric

vaccines are low-cost, commodity items, distributed throughout the world including the developing nations through programs run by organizations such as the World Health Organisation (WHO). It is in the adult sector that scope for market development is most clearly apparent, although new pediatric vaccines are also appearing. Vaccines have come back into the R&D programs of major companies (including Sanofi-aventis, GlaxoSmithKline, Merck and Wyeth) in the first decade of the century, as a result of scares about avian influenza, bioterrorism and new emerging infections like swine flu. In addition the introduction of cancer and rotavirus vaccines has greatly expanded the vaccine market.

Table 8a Worldwide human vaccine market (USD billion), 2007-2013

	2007	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**
Total Vaccine Market ($bn)	19.90	22.20	24.95	28.15	31.90	36.00	40.53
Growth (%, year-on-year)		12	12	13	13	13	13
CAGR (%, 2007-2013)							12.6

Source: visiongain, 2008

Notes: Data based on ex-manufacturer prices, 2007 figures are actual sales, other years are forecasts

Table 8b Worldwide human vaccine Market (USD billion), 2014-2023

	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Total Vaccine Market ($bn)	45.30	50.53	55.97	61.43	67.56	72.62	78.09	84.01	90.43	97.38
Growth (%, year-on-year)	12	12	11	10	10	7	8	8	8	8
			CAGR (%, 2013-2018) 10.8%					CAGR (%, 2018-2023) 7.6%		

Source: visiongain, 2008

Notes: Data based on ex-manufacturer prices, 2007 figures are actual sales, other years are forecasts

Vaccine sales claimed a lion share which is 10.4% of the total anti-infectives market. There are several key players for vaccines in the global market. The "big five" includes Merck & Co, Wyeth, Sanofi-Aventis, GSK and Chiron. Merck & Co's vaccines franchise is set to grow from 5-10% annually. The growth is driven predominantly by high-income country demand for higher priced vaccines, not volume. Increasingly, high income country vaccination schedules are diverging from those in low and middle income countries. This trends threatens one of the bases for tiered pricing, whereby high-income and low income countries bought the same products, but high income countries' pricing covered most of the production cost. The companies mentioned above, collectively, may have spent at least USD1billion per year on R&D. This growth depends mostly on the launch and success of pipeline products for HPV (cervical cancer), zoster (shingles) and MMR-varicella. Wyeth's major sales is from its pneumococcal vaccine, Prevnar. However, Wyeth has a very thin vaccine pipeline with no products

due for launch. Meanwhile, GSK is the leading company in the vaccines market, with sales of more than USD 2billion per year worldwide. GSK also has the most extensive pipeline of the five leading players. The most promising pipeline candidate is Cervarix for HPV (cervical cancer). Sanofi-Aventis is trailing marginally behind GSK. Recently in the 4th Quater 2010, Sanofi-Aventis launched clinical trial phase II in Malaysia and South-East Asia for its new dengue vaccine. Meanwhile, Chiron is the 5th largest vaccines company, and its major product is Fluvirin, an influenza vaccine.

Vaccine production economics are highly volume sensitive, with an average 60% of fixed costs at the manufacturing level and 25% fixed cost on per batch basis. Scale is therefore a major cost driver. Whilst there is wide variation in the costs to produce different vaccines, many of the factors explaining these differences are subject to buyer influence. For existing vaccines, multi-dose packaging and making appropriate use of those lower cost suppliers that are both economically viable and meet quality standards enhances affordability. For new vaccines, influencing batch size decisions during plant scale-up will enhance affordability.

In Malaysia, GSK has captured the most for sales in pediatric vaccines for the government/public market. Whilst the vaccine market is currently dominated by vaccines for the pediatric population, a major growth driver for the future is likely to be increased vaccination amongst the adolescent and adult population. Developmental vaccines for booster or catch-up immunization against diphtheria, tetanus and pertussis (DTP) are one example, as is the development of a zoster (shingles) vaccine by Merck & Co. Another growth driver is likely to be the launch of vaccines for sexually transmitted diseases (STDs). Examples are GSK's Cervarix

and Merck's HPV vaccine for HPV (cervical cancer), GSK's Simplirix for genital herpes, and several early-stage HIV vaccines.

It is forecasted that the booming vaccines market will double (or more) in the decade starting in 2010. Aside from the new and more powerful vaccines that have been hitting the market, physicians and pediatricians have been promoting a more proactive use of vaccines for the broad population. Governments have proven to be willing to accept much of the cost for vaccines since this constitutes an effective long-term strategy to reduce the cost of more expensive therapies needed to treat the sick.

Table 9 Vaccine preventable human disease statistics

Disease	**Estimated Worldwide Cases**	**Estimated Worldwide Fatalities**	**Selected Worldwide Vaccination Statistics**
Cervical cancer/ HPV	500,000 (new cervical cancer 2006) 32 million for genital warts (2005)	250,000 (cervical cancer, 2006)	?
Chickenpox & Shingles	10 million (chickenpox, 2007) 2.5 million (shingles, 2006)	10,000 (chickenpox, 2007)	?
Cholera	240,000r (2006)	6000r (2006)	
Diphtheria	4000r (2006)	5000r (2002)	79% of 1-year olds (worldwide, 2006)
Haemophilus influenzae type b (Hib)	4 million (2006)	400,000 (2006)	22% of 1-year olds (worldwide, 2006)

cont. Table 9

Hepatitis A	1.5 million clinical cases (2003)	5000 (2003)	?
Hepatitis B	350 million chronic carriers (2002)	600,000 (2002)	60% of 1-year olds (worldwide, 2006)
Influenza	1 billion (2005)	400,000 (2005)	
Japanese encephalitis	50,000 (2006)	15,000 (2006)	
Measles	20 million (2006)	200,000r (2006)	80% of 1-year olds (worldwide, 2006)
Meningococcal diseases	500,000 (2002)	50,000 (2002)	?
Mumps	20-30 million (2007)	2000-3000 (2007)	?
Pertussis	60 million (2007)	350,000 (2007)	79% of 1-year olds (worldwide, 2006)
Polio	2000 (2006)	<1000 (2002)	?
Rotavirus diseases	> 1 billion (2006)	500,000 (2006)	?
Rubella	>100,000 cases of CRS* (2006)	?	?
Streptococcus pneumoniae infections	>20 million (2007)	1 million (2007)	?
Tetanus	500,000 (2007)	50,000 (2003)	70% of pregnant women (worldwide, 2006)

cont. Table 9

Tick-borne encephalitis fever	13,000 (2007)	50 (2007)	?
Tuberculosis	8 million clinical cases (2006)	1.6 million (2006)	87% of infants (worldwide, 2006)
Typhoid	17 million (2000)	600,000 (2000)	?
Yellow fever	200,000 (2006)	30,000 (2002)	48% of infants in at-risk areas (2006)

Source: visiongain and WHO, 2008
Notes: r = number of cases reported to WHO,. All other data are based on estimates.
* CRS = congenital rubella syndrome

Table 10 Selected human diseases currently without a vaccine

Disease	**Cases per year**	**Estimated Fatalities/Year**
Cancer*	25 million (2005)	8 million (2005)
Dengue fever	50 million (2007)	10,000 (2007)
Epstein-Barr virus	95% of world population infected (2007)	?
Helicobacter pylori infection	3 billion infected (2007)	?
Hepatitis C	170 million infected and 3-4 million new cases (1999)	?
Hepatitis E	>100,000 (2007)	>1000 (2007)
HIV/AIDS	33 million infected (2007)	2 million (2007)
Malaria	500 million clinical cases (2005)	1-3 million (2005)

cont. Table 10

Nosocomial infections, e.g.: • Clostridium difficile • Staphylococcus • Pseudomonas aeruginosa • Enterococcus	C. difficile:150,000 (US and Europe, (2006) MRSA: 100,000 (US, 2005)	MRSA: 20,000 (US, 2005)
Respiratory infections non-vaccine preventable), e.g.: • Group A Streptococcus • Group B Streptococcus • Respiratory syncytial virus • Parainfluenza • Adenoviruses	>100 million (2007)e.g. >18 million cases of severe group A Streptococcal disease (2007); 64 million RSV infections (2007)	>10 million (2007), e.g. >500,000 deaths from severe group A Streptococcal disease (2007); 160,000 deaths from RSV (2007)
Roundworm and hookworm Sexually-transmitted diseases • Chlamydia • Herpes simplex virus • Gonorrhoea, • Syphilis • Cytomegalovirus	>1 billion (2006) e.g. 100 million new chlamydia infections (2007)	150,000 (2006)
Tobacco use	1.25 billion smokers (2005)	5 million (2005)
West Nile virus infections	4000 (US only, 2007)	100 (US only, 2007)

Source: visiongain, 2008
Notes: some types of cervical cancer are vaccine-preventable

Veterinary vaccines

The market for veterinary vaccines is spread across species but it is limited in size and the development of vaccines is becoming more complex and expensive.The global veterinary vaccines market is rapidly growing at CAGR of more than 6%, from USD3.8 billion in 2008, USD4 billion in year 2009 and is projected to reach USD5.6 billion by year 2015. Forty-one per cent of the market was based in the Americas, 37% in Europe and 22% across the rest of the globe. Vaccines and biological constitute 14% of the major sector of the animal heath market. Others are pharmaceuticals (51%), medicinal and nutritional products (35%). Key factors driving growth include growing number of diseases in animals, increasing public awareness, and technological advancements in biotechnology research. Further, the ability of the vaccines to promote growth, develop immunity against diseases and lower the rate of mortality in the animals is driving sales of veterinary vaccines.

In relation to biological (including biopharmaceuticals), vaccine research targets the three major market sectors, cattle, pigs and poultry. Vectored vaccines and marker vaccines will become widely available. Broad spectrum anti-mastitis vaccines for dairy cattle, anti-coccidia vaccines for poultry and improved multi-valent vaccines for cattle, pigs, and poultry will be primary targets. Other major targets are the development of anti -parasite vaccines for ticks, nematodes and liver fluke. In 1994 the world's first commercially available cattle tick vaccine was launched in Australia. Finally food safety vaccines are expected to emerge for use against organisms of public health significance such as Salmonellae, Campylobacter and Listeria. Advances in delivery system technology will be highly significant. Sustained release anti-microbials and anti-parasitics are likely to be offered and oral delivery systems could replace the injection of many vaccines.

Other than protecting animals, animal vaccination helps to prevent the spread of disease to humans (e.g. salmonella vaccination ensures high quality food is produced from healthy animals) and helps to protect the environment. Vaccines, coupled with diagnostic tests, eradication programmes and surveillance, help to eradicate diseases, e.g. foot and mouth disease (FMD), rabies and Aujeszky's disease in many EU countries. Vaccination also help to reduce the annual 17% loss of production associated with disease in animals.

New adjuvants

Traditional vaccines normally employed whole, attenuated or inactivated disease causing agents,. Those vaccines were formulated with adjuvants and that to induce a more potent and persistent immune response. However, to reduce the risk of adverse reactions, most of the new vaccines under development are based on well-defined molecular immunogens. Molecular vaccines include proteins, peptides, lipopeptides, plasmid DNA, and recombinant viruses based on viral vectors known to be safe in humans. However, these vaccines are generally not as immunogenic as traditional vaccines. New vaccine targets often require induction of strong cellular responses, including enhanced production of T helper cells and sometimes cytotoxic T lymphocytes in addition to antibodies. Conventional adjuvants based on aluminum salts mainly induce antibody responses, and discovering new adjuvants is crucial for the development of vaccines that require cell–mediated responses. A rational approach to adjuvant development has been driven by improved understanding of the control mechanisms in the immune system, and the interplay between the innate and the acquired immune response. In particular, the role of toll-like receptors (TLRs) in recognizing pathogen-associated molecular patterns and the ability to stimulate these receptors using a range of new

agonists of varying specificities has significantly advanced adjuvant development. Several TLR agonists have been studied as vaccine adjuvants in clinical studies. CpG oligodeoxynucleotide (ODN), a TLR9 agonist, was shown to be a potent adjuvant of both humoral and cell-mediated immunity in human studies. Monophosphoryl lipid A (MPL), a TLR4 agonist, has been shown to induce both antibody and T-cell responses. It was licensed as an adjuvant for hepatitis B vaccine non-responders in Europe.

In summary, new and improved adjuvants will bring the following advantages to vaccines:

- The ability to make existing inactivated vaccines more potent
- Ability for antigen-sparing,
- Stimulation of T cell immunity,
- More rapid immunity and longer-lasting immunity
- Expanded opportunity for development of therapeutic vaccines.

A key hurdle for new adjuvants is the need for clinical trials for new adjuvant-antigen combinations, in order to meet stringent regulatory requirements. Therefore, the benefits of incorporating any adjuvant into vaccines will need to be balanced against any increased risk of toxicity or side-effects

Cancer vaccines

The idea of using therapeutic vaccines against cancers is long-established, and advances have been made over the past few years in developing cancer vaccines using whole-cells, proteins or peptides, plasmid DNA, and viral vectors with new adjuvants. Natural or synthetic peptides and recombinant proteins as vaccines targeting

tumor-associated antigens have shown promising results in humans. A peptide vaccine targeting melanoma melanocyte differentiation antigens (MART-1, gp100, and tyrosinase), was shown to elicit immune responses and prolong relapse-free survival. Tumor cell vaccines can be generated from either the patient's own tissues (autologous) or other sources (allogeneic). Dendritic cells can be loaded with tumor antigens through the addition of tumor antigens to the culture media, either through incubation with autologous or allogeneic tumor lysate, gene modification with tumor antigen cDNA or autologous tumor mRNA, or creation of tumor cell–dendritic cell hybrids. A company, Dendreon, has developed a vaccine against prostate cancer prepared from a patient's own monocytes and then loaded with a tumor antigen (a fusion protein of full-length PAP and GM-CSF). In hormone-refractory prostate cancer patients treated with the vaccine, the median survival was significantly longer than placebo. An important caveat to the foregoing is that cancer vaccines are mostly in the early research stage; breakthroughs will depend on an increased understanding of what tumor-specific antigens are expressed during the initial tumor development stage.

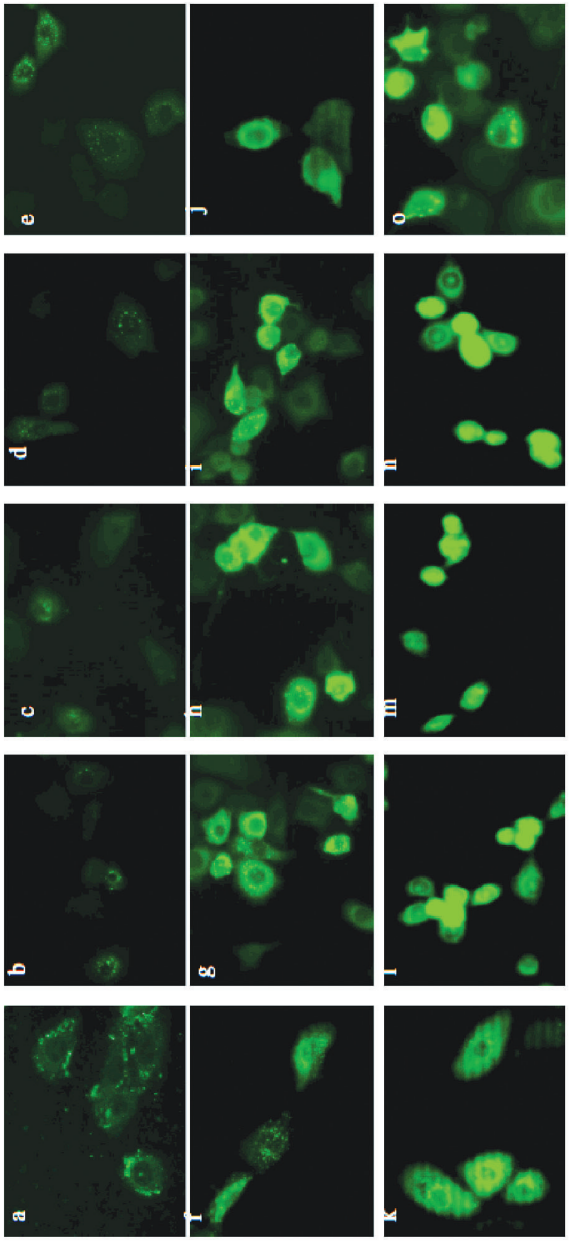

Figure 4 Immunofluorescence staining of cancer cells. Cancer cells injected with 2 mg/ml of purified MBP protein, to study the potential effects of anti-cancer protein in cancer cells.

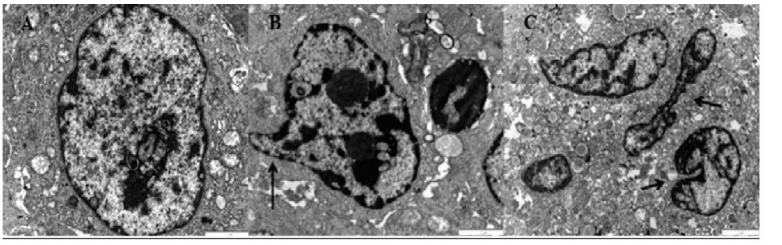

Figure 5 Transmission electron micrograph profiles showed left: normal nucleus of cancer cells (X5500), center & right: VP3 (chicken anaemia virus polypeptide 3)-transfected cancer cells (x 7700) - the features of apoptosis showed the shrinkage of nuclear membrane and "disintegration" resulting cancer cell death.

Cervical cancer and human papillomavirus (HPV)

HPV vaccines offer protection against the pathophysiological effects of HPV infection and HPV-infection-induced cervical cancer. Cervical cancer is the second most common cause of death among women with 470,000 new cases reported every year, leading to 233,000 deaths annually. HPV is a sexually transmitted virus, and it is estimated that nearly 50% of sexually active people will contract it at some time in their lives. In most cases, the viruses are neutralized by the immune system over a period of two to three years. In the others, HPV causes genital warts, which may increase in number and possibly turn cancerous. Nearly 90% of all cervical warts are caused by low-risk varieties of HPV, namely types 6 and 11, while 70% of all cases of cervical cancers are caused by the high-risk types 16 and 18. Vaccination is the best solution to HPV infection and its effects, as no cure exists.

Vaccine development for immunosterilisation

ZP3 protein is an extracellular elastic coat that surrounds the vitelline membrane of mammalian oocytes. The function of ZP3 includes serving as sperm receptor inducing the acrosome reaction, and preventing polyspermy. Therefore, due to its critical roles in fertilization, it has been selected as candidate antigen for immunocontraceptive vaccine.

ZP3 DNA vaccine

The recombinant constructed is comprised of a mammalian expression vector containing gene sequence encoding rat ZP3 protein, which in turn stimulates the development of specific cellular and humoral immune responses directed against the destruction of self-ZP3 protein of oocytes.

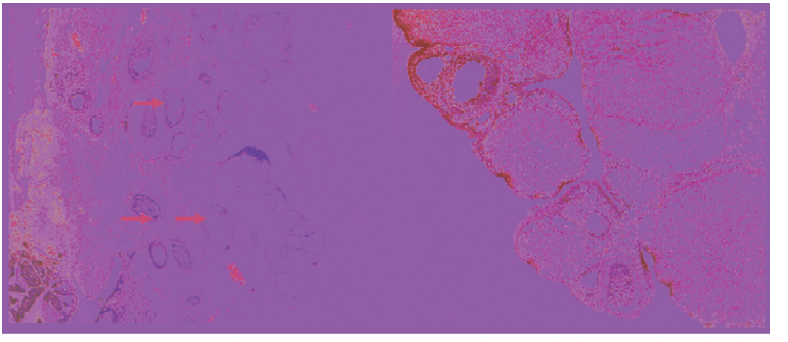

Figure 6 Experimental immunosterilization of rats with anti-ZP3 DNA vaccine. Left: Normal ovarian section showing follicular development at different stage. Right: Ovarian section of an animal vaccinated with ant-ZP3 DNA vaccine containing low amount of functional follicles that producing ova.

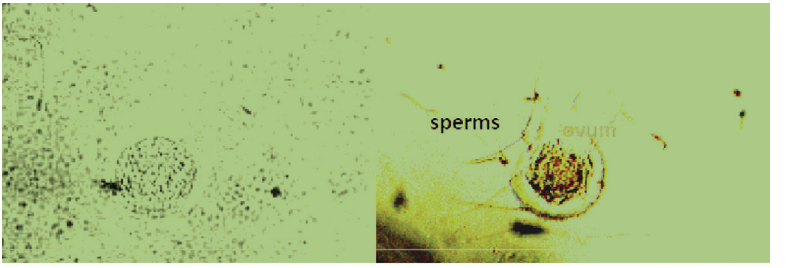

Figure 7 Experimental immunosterilization of rats with anti-ZP3 vaccine. Left: No sperm bind the ovum treated with anti-ZP3 antibody. Right: A sperm directly bound/attached to the ovum un-treated with anti-ZP3 antibody

Recombinant adenovirus-ZP3 vaccines

Recombinant adenovirus currently is used for a variety of purposes, including gene transfer *in vitro,* vaccination *in vivo*, and gene therapy. Several features of adenovirus biology have made such viruses the vectors of choice for certain of these applications. For example, adenoviruses transfer genes to a broad spectrum of cell types, and gene transfer is not dependent on active cell division. Additionally, high titers of viruses and high levels of transgene expression generally can be obtained. The adenovirus vector system uses a human virus as a vector and human cells as a host. It therefore, provides the ideal environment for proper folding and exact post-translational modifications of human proteins.

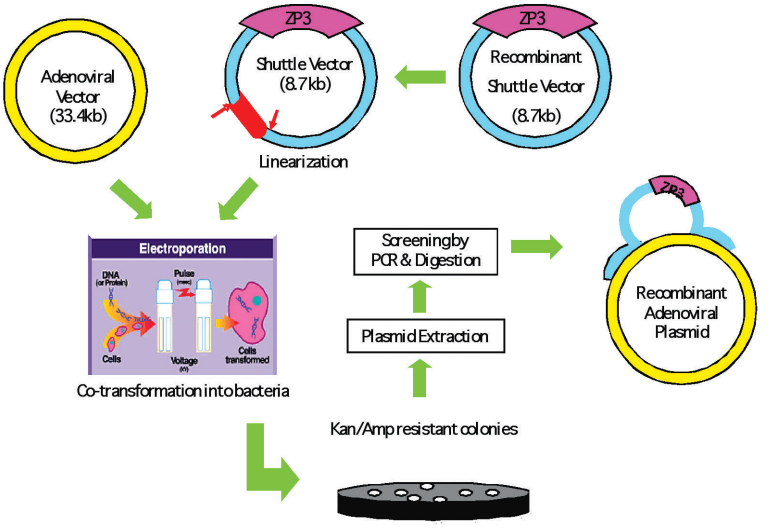

Figure 8 Cloning the gene of interest into adenovirus.

Therapeutic vaccines

The term 'therapeutic vaccine' is a paradoxical expression, as vaccines have always been designed for prophylaxis of diseases in healthy individuals. Therapeutic vaccines are designed to improve the immunity status of a patient suffering from a pathological condition against which the body has insufficient immune control or has lost it entirely. These vaccines "teach the immune system" to re-tackle the pathological state that originally led to the compromised immune system. Of late, this utopian conception has captured the imagination of researchers, in both public and private organizations. The concept of therapeutic vaccines has been extended to several other indications, including those that do not result in a compromised immune system. It is also under investigation in lifestyle disorders such as smoking and narcotic abuse. The biggest risk of therapeutic vaccines is the probability

of re-infection, which might lead to catastrophic consequences. Therapeutic vaccines in general target a common shortcoming of prophylactic vaccines: the inability to generate sufficient cell-mediated immunity. There are several approaches being investigated to generate sufficient levels of humoral and cell-mediated immunity in a disease-affected individual. Based on the current approaches, therapeutic vaccines may be classified as follows:

Antigen/whole cell vaccines

Vaccines containing inactivated whole cells or antigens or parts of antigens (idiotypes) intended to stimulate an immune response against the target organism or pathological state. Most research on such vaccines occurs with reference to cancer, human immunodeficiency virus (HIV) infection, malaria and so on.

Dendritic cell vaccines

Dendritic cell (DC) therapy or DC vaccines are an emerging form of immune therapy currently conceptualized for cancer and acquired immunodeficiency syndrome (AIDS). DCs are immune cells that play a significant role in the recognition, processing and presentation of foreign antigens to the T cells. However, in most cases these are not usually present in sufficient quantity to provide a suitable immune response. DC therapy thus involves the harvesting of blood cells such as monocytes or macrophages from a patient and turning them into DCs. The processed. DCs are then utilized as vectors for the delivery of antigen. The methodology thus provides dual advantages, both amplifying dendrite cell numbers and delivering antigens.

Cytolytic viral vaccines

The concept of the cytolytic viral vaccine is currently being investigated for the treatment of cancer. The idea originates from the observation of tumor regression following viral infection or rabies vaccination. Therefore, the ability of the therapeutic virus, based on the concept of maintaining a non-pathogenic status, is of utmost importance. The idea, however, faces several impediments in terms of the availability of an ideal viral particle for vaccine development. There has been little success reported from research on this front to date. The Phase I trials of the ONYX- 015 virus vaccine, investored by the National Cancer Institute, have been cancelled due to its lack of efficacy in killing p53-based cancer cells as originally proposed.

Translational medicine

Translational medicine (or sciences, TS) is a term meant to convey research that is applicable from the bench or laboratory to the "bedside". But what does this really mean? There are many diverse answers would be given by different scientists. Some would define TS as an effort to bring novel therapeutic strategies to patients based on relevant experimental data. Others would use TS interchangeably with the term "Personalized Health Care", both of which refer to the process of applying molecular insights from the laboratory into a clinical setting. The bottom line is that the concept of TS is really pointing to a vision of bringing the right drug to the right patient through intelligent investigation of a patient's profile: whether it be a molecular profile or some other differentiating factor.

Superficially, this might sound like an easy approach, but the reality is that nothing is as simple as it sounds–especially given the diverse nature of biologic systems. Members of a traditional Research or Discovery group rarely focus solely on answering

questions that would make a direct and immediate clinical impact, such as patient selection or monitoring molecular pathways associated with drug target interaction that would help select patients, or the most appropriate drug dose level or schedule. On the other hand, Medical Doctors are often focused on clinical endpoints where a combined clinical and molecular approach may actually transform and accelerate a program. TS is committed to bringing the two groups together. On a daily basis, we ask the following basic questions:

- What specific biological events or molecular pathways play a role in certain diseases?
- What biomarker(s) can we monitor to assess target neutralization in the clinics?
- How can we best use this information to discover and develop new therapeutics and associated diagnostics that will help with patient selection?

As with any new concept or approach, it takes time to implement. In the end, the added value and benefit that TS affords to drug development will ultimately be reflected by the patients themselves

SWOT Analysis of Vaccine Market

Source: visiongain, 2008

Strengths

- High-cost effectiveness and efficacy of vaccines
- New therapeutic and addiction vaccine sectors

- New vaccine technologies, e.g. recombinant DNA technology and novel adjuvants
- Novel vaccine formulations and more convenient vaccine delivery methods
- New high-margin vaccines backed by innovative marketing campaigns
- Low prospect for generic vaccine competition
- Personalised vaccines
- Opportunity for contract research and development, and manufacturing of vaccines in developing countries

Weaknesses

- Expensive vaccine research and development process
- Difficult regulatory approval process - large clinical trials and low toleration of side-effects
- Complex vaccine manufacturing process
- High barriers for new companies to enter vaccine market
- Vaccine market dominated by small number of large players

Opportunities

- Large unmet need for vaccines for currently non-vaccine-preventable diseases
- Expanding biodefence and pandemic-preparedness market
- Population increase, especially in developing countries, with high need for combating infectious diseases
- Growth of emerging economies

- Increased funding from governments for vaccination campaigns

Threats

- Anti-vaccine campaigns
- Lack of societal recognition of part vaccines play in public health
- Over-estimation by general public of side-effects associated with vaccines
- Difficulty in distributing vaccines, especially in developing countries
- Necessity to persuade governments and health insurers to reimburse vaccines at a satisfactory price

PATENT EXPIRY, GENERICS AND BIOSIMILARS

MAbs such as Herceptin and Rituxan/Mabthera, set to lose patent protection by year 2013/15. Based on the present high market price charged per patient (e.g. RM60,000 per course of treatment) the patent expiry will soon created a gold-rush effect to existing players for biosimilars. Globally, biosimilars market grew 5.9% to reach a value of approximately RM4.8 billion in 2012 with the top 10 players representing approximately 15% of the total market. What factors fueling the growth? It lies in the demand for the use of biosimilar in hard-to-treat disease areas such as cancer, autoimmune and healthcare cost containment. Meanwhile, European Medicines Agency (EMEA) has legalized a pathway for the approval of biosimilars in year 2006. As a result, the regulatory authority provides 10 years of patent protection to biologics. The limited scope of patent protection for biologics makes data exclusivity

periods is crucial for protecting capital investment in biosimilars. However, the US is still in the midst of considering a biosimilars approval pathway.

Interestingly, a major strength of the vaccine industry is lack of generic competition. Unlike generic drugs, for which there is a booming market, generic vaccines will not gain significant market share. Vaccines, along with biopharmaceuticals such as monoclonal antibodies, interferons and insulin, are protected from generic competition by a number of factors:

Although some vaccines have expired patents, numerous patents will protect many of the current top-selling vaccines.

Even when patents have expired, a prospective generic vaccine manufacturer must face the expensive process of regulatory approval. In the major market e.g. US FDA currently does not have a process for the review and approval of generic versions of biologic products. In markets where there is a regulatory path for biologics, cost savings from generic vaccines are likely to be much less significant than cost savings from non-biologic generic drugs. This is owing to the complexity of the vaccine manufacturing process.

Finally, potential generic vaccines might face competition from more efficacious branded follow-on vaccines. All these factors will conspire to limit the market for generic vaccines. Generic vaccines will remain limited to certain mass market traditional prophylactic vaccines. These will be manufactured increasingly by a small number of specialised contract manufacturing companies, most probably in emerging market economies.

Table 11 Comparisons between generics and biosimilars

	Generics (Pharmaceutical)	**BioSimilar (Biopharmaceutical)**
Product features	Small molecules	Large, complex molecules requiring a proper drug delivery system
Production	Produced by chemical synthesis	Produced through intensive genetic engineering methods
Development	Low technology barrier	Significant R&D (genetic engineering, cell lines etc.)
Clinical Trials	Does not require costly clinical	Extensive clinical trials, including Phase I trials to prove bioequivalence and Phase III, to prove bioequivalence and substitutability and substitutability
Regulation	Proper regulatory framework	Only Europe has a proper regulatory exists for most of the developed pathway for biosimilars approval; generic markets the US is still debating over the legislation
Marketing	Generics are sold at large price differential	Sold at low price differential, discounts (up to 95%) to the approximately 25%–35%, to the innovator drug as the cost of innovator drug manufacturing is low
Physician requirement	Limited detailing to physicians	Detailing to specialist and physicians required

REGULATORY REGIME AND INTELLECTUAL PROPERTY (IP)

National Regulatory Authority (NRA)

The main regulatory authority in Malaysia is National Pharmaceutical Bureau (NPCB), supported by Drug Control Agency (DCA), under the auspices of the Ministry of Health. Five items of legislation form the basis for market regulation: The Poisons Act 1952 (Revised 1989); The Sales of Drugs Act 1952 (Revised 1989); The Medicines (Advertisement and Sales) Act 1956 (Revised 1983); The Registration of Pharmacists Act 1951 (Revised 1989); and The Dangerous Drugs Act 1952 (Revised 1980). Similar to FDA (USA) and EMEA (Europe), NPCB is responsible for registration applications for drugs and cosmetics; licensing importers, manufacturers and wholesalers; post-marketing safety surveillance; and the monitoring of adverse drug reactions. NPCB is to ensure the safety, quality and efficacy of pharmaceuticals in Malaysia. NPCB-approved locally-made drugs are also accepted in Organisation for Economic Co-operation and Development (OECD) countries, illustrating the quality of generic medicines produced in Malaysia. Drug registration processes may take 1-2 years duration.

Malaysia registered some 207,911 medicines in total, of which 154,507 are imports, according to the Ministry of Health's figures released in January 2009. The authority claim that any drug in a pharmaceutical dosage form for human or animal use must be registered with the agency. This includes products that alleviate, treat or cure diseases; products that diagnose a disease; anaesthetics; and products that maintain, modify, prevent, restore or interfere with normal physiological functions. The regulation does not apply to diagnostic agents and test kits for laboratory use; non-medicated medical and contraceptive devices; non-medicated bandages and

surgical dressings; and instruments, apparatus, syringes, needles, sutures and catheters.

Malaysia has supported the alignment of domestic procedures with international norms, such as to harmonise procedures within the ASEAN region. The Malaysian Pharmaceutical Product Working Group (PPWG) is responsible for the task. Currenlty, 10 ASEAN countries have adopted the common documents on technical requirements, the dossier on quality, safety and efficacy, administrative data and glossary, and the guidelines on analytical process validation.

Under Regulation 12(1) of the Poison Regulation 1952, where any poison (prescription and nonprescription medicines) is sold or supplied as a dispensed medicine, or as an ingredient in a dispensed medicine, the container of such medicine shall be labelled, in a conspicuous and distinct manner, with: the name and address of the supplier or seller; the name of the patient or purchaser; the name of the medicine; adequate directions for the use of such medicine; the date of delivery of such medicine; and where such medicine is sold or supplied.

In October 2005, the Ministry of Health issued the requirement that all registered pharmaceutical products be labelled with a Meditag, a hologram security patch. The Meditag scheme was introduced in early 2005 in an effort to attack unregistered copy drugs, counterfeits and other healthcare products. Under the guidelines, anyone who fails to abide by this law will be subject to a fine, imprisonment or both. First-time offenders will be fined up to RM25,000 and/or jailed for up to three years. Any corporate entity failing to abide by this law will also be charged a fine of RM50,000 for firsttime offenders, or RM100,000 for subsequent offenders. The Meditag scheme will involve the participation of enforcement officers, who will conduct visual scans of the symbols and markings

on the Meditag device, as well as verify the manufacturer's serial number. The authenticity of the hologram can be confirmed by examining it with a special decoder and a microscope.

Rules covering veterinary medicines were implemented in 2007 and plans have been drafted for active pharmaceutical ingredient (API) laws. The API regulations will attempt to combat the usage of sub-standard and un-approved raw ingredients, thereby minimising the problem of adulterated medicines in the supply chain.

IP and Compulsory Licensing in Malaysia

Malaysian government has made several major revisions on patent law e.g. in year 2001 and 2003. Despite tremendous efforts to improve patent protection in Malaysia, the amendment has yet to satisfy international drug manufacturers. Malaysian government has guaranteed 20 years of protection for pharmaceutical patents. In addition, the government has also implemented the following legal provisions: 1) The limited manufacturing, use and sale of a generic drug before the expiry of the original's patent should no longer be considered patent infringement; 2) Provisions allowing the licensing and production of medicines by the government under certain conditions, without the patent holder's consent. Meanwhile PhRMA (USA) has criticised the Malaysian government on several issues: the high level of counterfeiting products in the Malaysian market despite the introduction of holograms on pharmaceutical packaging), the difficulty in applying process patents, the lack of data exclusivity (which has not been aligned with the TRIPS agreement) and the overall poor standard of regulatory enforcement, the lack of patent linkage as part the registration process (which has led to instances of generic products being launched while original patents are still in effect), the need for products bought by the government to be listed on a purchases list (the 'Blue Book', which requires a

lengthy application process i.e. 24 months) due to the infrequent meetings of the supervisory body, local companies often obtaining market authorisation faster than imports, and the bioequivalence for generics is limited to a number of therapeutic areas, leading to further accusations of bias against foreign producers. Estimated annual losses related to lax patent protection and other IP issues in 2005, is about 8.4% of total sales Malaysian government has changed data exclusivity laws for new chemical entities to five years and for new indications from the date of approval in the country of origin to three years, this still falls short of international requirements, as Malaysian approval is often delayed. Malaysia has already issued compulsory licences to Indian drugmaker Cipla for a supply of anti-retrovirals (ARVs) in the management of HIV/AIDS. The original inventor drug suppliers were US-based Bristol-Myers Squibb's didanosine and UK firm GSK's zidovudine and lamivudine + zidovudine. This has drive down prices significantly, from RM 1,200 to RM200, then RM150 per month/patient. Such action by our government has made ARVs affordable to the vast majority of the population and it affects the profit margin of innovator drugs significantly.

MALAYSIAN MARKET AND BIOPHARMACEUTICALS

The Malaysian biopharmaceutical market is relatively underdeveloped. The market is based on imports of branded and patented products (mostly from the US, Japan and Germany). Slightly more than 0.5% of GDP is from spending on pharmaceuticals. The overall market value is about RM 4billion and expected to increase 7% per year. Imports will continue to dominate the Malaysian market, and the big market share will be with MNC.

Malaysian government has prompted new regulations targeting to stimulate the generics market. If this is going to be a success, the

government is expected to significantly lower down their spending (minimum average 50% of selected innovators' drugs) on healthcare (supported by studies conducted by School of Pharmaceutical Sciences, Universiti Sains Malaysia, 2009). However, the response from industry players in Malaysia insofar has been very modest. Generic products are poorly marketable compared to well branded innovators' drugs were viewed by practitioners as superior in quality. However, as patent protection on about 50 products, with high sales figures, will expire within the next 5 years, generics are expected be hot products to be produced manufacturers and this is in line with initiatives declared under Economic Transformation Programs (ETP) 2010/11. The rising quality of generics, cost-containment needs and implementation of the ASEAN Free Trade Area (AFTA) agreement, with products from signatory countries to be exempt from import barriers and tariffs are expected to be the main drivers for generics/biosimilar. Meaning, existing players who are early prepared will be in the best position to capture the market. However, the government's plan to introduce price ceilings on essential drugs would be negatively reflected in the value of the generics/biosimilar. The market value of generic products are expected to grow at a CAGR of 10.51% to reach RM1.67billion at the expense of patented drugs.

Table 12 Generics Market and Forecats

	2004	**2005**	**2006**	**2007**	**2008**	**2009f**	**2010f**	**2011f**	**2012f**	**2013f**
Generics/ biosimilar market (RM)	0.713	0.770	0.839	0.903	1.031	1.131	1.231	1.409	1.562	1.699

cont. Table 12

Generics/ biosimilar market as % total market	24.0	24.3	24.6	24.8	25.0	25.9	26.4	27.6	28.1	28.5

f = forecast.
Source: IMS Health Asia, BMI

SWOT for Biopharmaceutical in Malaysia

Source: Business Monitor International Ltd , 2009

Strengths

- Increasingly progressive government policy, aimed at attracting
- Improving local manufacturing standards
- Commitment to biotech sector development
- Robust market growth in recent years
- Absence of price controls in the private sector
- Sizeable generics market, founded on low patient purchasing power and traditionally lax patent laws
- Prescribing and dispensing presently dealt with by general practitioners, boosting
- overall values of the prescription market
- Manufacturing of halal medicines improving access to other Islamic markets in the region and wider

Weaknesses

- Markedly behind South Korea, Singapore and Taiwan in terms of pharmaceutical expenditure and foreign direct investment (FDI)
- Recent reform aimed at increasing generic product development worsening operating conditions for multinationals
- Local manufacturing output comprising predominantly inexpensive, basic medicines
- Market reliant on imports, particularly at the hi-tech end of the scale, pressuring government finances

Opportunities

- Generics sector as an integral factor of market growth
- Exports growing in the face of rising regional and global demand, as well as increasing trade links
- Strict government drug pricing policy heavily biased towards local drug producers
- Increasingly sophisticated pharmaceutical demand
- Government desire to prevent and contain disease outbreaks
- ASEAN harmonisation encouraging the adoption of Western regulatory standards and the improvement of intra-regional trade
- Investment in the biotech sector development supported by government initiatives
- Malaysia becoming an attractive location for medical tourism
- More transparent legislation and the attraction of foreign investment

- Pending FTA with a number of key trading partners
- Planned investment in the expansion of medical facilities
- Malaysia offers a considerable contract manufacturing opportunities

Threats

- Existence of a significant counterfeit drugs
- Encouragement of parallel trade
- Increased focus on internationally recognised norms and legislation to disadvantage of local players
- Possible introduction of price ceilings on essential medicines
- Government seeking compulsory licenses for patented drugs

MANUFACTURING OF BIOPHARMACEUTICALS

The Stages of Biopharmaceutical Development

The pharmaceutical industry is the most highly-regulated industrial sector. No medicinal product can be placed on the market without receiving prior authorization from the regulatory authorities responsible for evaluating the quality, safety and efficacy of the product. All pharmaceuticals on the market are required to be manufactured in premises which are inspected to ensure compliance with strict Good Manufacturing Practices (GMP).

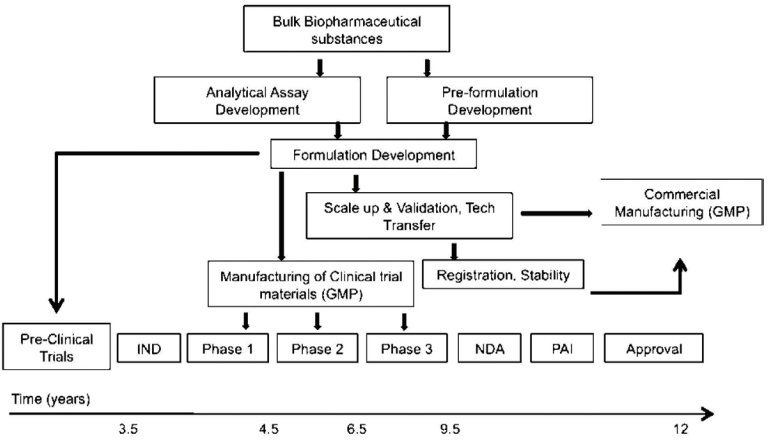

Figure 9 Biopharmaceutical drug development and milestones towards commercialization

Preclinical and Stages of Clinical Trials

Pre-clinical trials

Pre-clinical research consists of laboratory screening of molecules (bioassays and animal tests) to evaluate their therapeutic potential and toxicity.

Phase I clinical trials

Studies usually conducted in a small number of healthy volunteers. They aim to establish safety at a given dose level and information regarding absorption, distribution, metabolism, excretion, including bioavailability and the pharmacological aspects of the drug's action. For some conditions (e.g. cancer) Phase I trials will be carried out only in patients with the target disease.

Phase II clinical trials

Studies conducted in a limited number of patients suffering from the target disease. These may initially be open studies providing evidence of general activity and efficacy, establishment of an effective dose range and frequency of administration. Patients will be carefully monitored for all possible side effects. Later Phase II studies will use larger numbers of patients and will generally be double-blind studies making comparisons with a placebo.

Phase III clinical trials

Studies involving large numbers (several hundred to several thousand) of patients with the target disease and often a long period of administration. There will be comparisons with established medicines for the target disorder. Such studies will provide further documentation of any side effects, toxicity and general safety of the medicine and may be used to check for interactions with any other medications patients are likely to receive concurrently.

'Phase IV'

Post-marketing surveillance scrutinising new drug usage and clinical trials carried out after marketing. These studies aim to determine whether previously unrecognised adverse effects or abuses occur, or whether there is a change in the occurrence of known adverse effects. Such work may also reveal if there are differences in effectiveness of the medicine for labelled indications under circumstances of widespread usage or if new therapeutic indications of the medicine can be recognised. The definition excludes studies in support of marketing.

GMP Manufacturing Process

Once a production method is established and scaled up, biopharmaceuticals can be produced in bulk (large batches). This is done by growing host cells (if active proteins desired are expressed by mammalian cells or microbes) that have been transformed to contain the gene(s) expressing the protein(s) of interest in highly controlled conditions in large stainless-steel tanks also called fermenters. The cells are encouraged to propagate and stimulated to produce the target proteins through precise culture conditions that include a well defined balance of temperature, oxygen, acidity, media components and other variables ultimately influencing the cells behavior. After careful culture the proteins are isolated from the cultures, stringently tested at every step of purification, and formulated into pharmaceutically-active products.

The Upstream Process includes all processing steps from cell expansion from the origin master cell bank (MCB) through to the bulk product. The operations that include the expansion of the cell population (and viral population, if applicable) and the biosynthesis and harvest of the product comprise the major components of the Upstream Process. These steps usually occur in roller bottles and bioreactors, but may also occur in whole plants or animals (transgenics) or in micro-scale vessels (cell and gene therapies). The Downstream Process includes all processing steps and operations from the bulk product through to the final product. Downstream operations involve the separation of the therapeutic product from the culture medium via filtration, chromatography techniques, followed by concentration, purification and formulation of the final product.

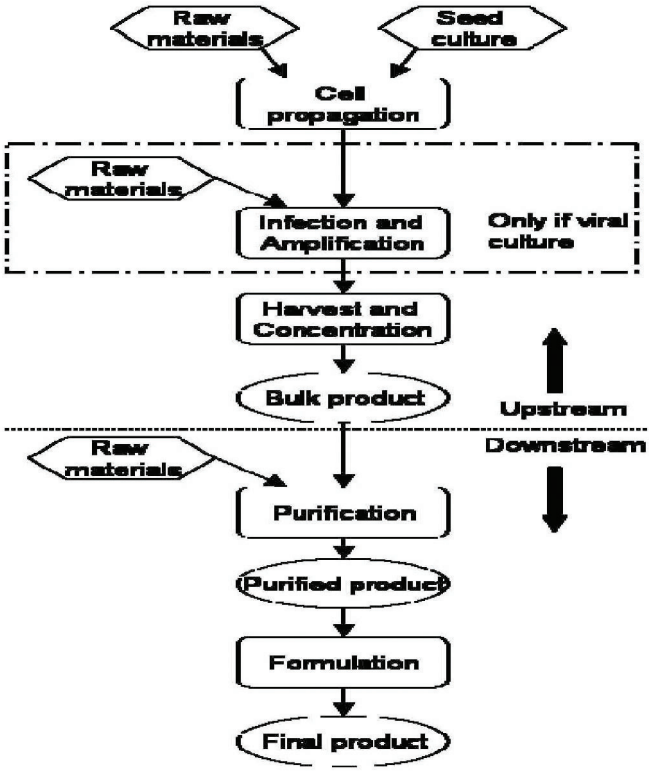

Figure 10 Biopharmaceutical drug development and production scheme

Table 13 Examples of production methods for recombinant therapeutic proteins

Product	Clinical application	Company	Production method
Advate	Hemophilia	Baxter	perfusion
Aldurazyme	Mucopolysaccharidosis	Genzyme	perfusion
Erbitux	Metastatic colorectal cancer	ImClone	fed-batch
Fabrazyme	Fabry disease	Genzyme	perfusion
Humira	Rheumatoid arthritis	Abbott	fed-batch
Kogenate	Hemophilia	Bayer	perfusion
NovoSeven	Hemophilia	Novo Nordisk	perfusion
ProstaScint	Prostate Cancer Screening	Cytogen	perfusion
Rebif	Multiple sclerosis	Pfizer/Serono	perfusion
ReFacto	Hemophilia	Wyeth	perfusion
Remicade	Rheumatoid arthritis	Centocor	perfusion
ReoPro	Anticoagulation	Centocor/Eli Lilly	perfusion
Rituxan	B-cell nonHodgkin's lymphoma	Idec Pharmaceutical	fed-batch
Simulect	Immunosuppressive	Novartis	perfusion

cont. Table 13

Synagis	Prevention of RSV disease	MedImmune	fed-batch
Xigris	Severe sepsis	Eli Lilly	perfusion
Xolair	Metastatic colorectal cancer	Genentech/Novartis	fed-batch

The Importance of Process Integration

A successful and cost-effective biopharmaceutical process can only be developed if all areas involved have a broad understanding of the impact of upstream process decisions on all downstream steps. Close communication, particularly in the early phases ensures that holistic processes that consider the entire process stream are developed, rather than a series of locally optimized steps that have little synergy with one another. Improvements in one step can easily be lost downstream without adequate process integration. One form of process integration is the combination of downstream separation operations into single separation steps. Modifying the product by adding affinity or fusion tags, may allow selective purification. It is important not just to consider the affinity separation, but also to ensure that the product can be adequately separated, and determine whether the affinity component can be easily regenerated and reused. Process scientists aim to select a host expression system with great product yield and a contaminant spectrum that is most orthogonal to the product in terms of physical properties. Many biotechnology companies express the same product in multiple hosts at the same time and choose the best system based on several parameters - not just highest expression level. Hosts can be screened for product stability, growth kinetics, expression yields, ease of downstream processing and contaminant composition. It is often advantageous to take the time to improve the host rather than invest in additional capital equipment and additional separation steps to remove troubling contaminants. Modern proteomics and genomics techniques allow the expression scientist to build a better host. This requires the downstream processing scientist to be involved in the host selection process to give input on desirable characteristics from a processing perspective. The culture type and operating mode can heavily impact downstream purification. Therefore the downstream

process needs to be flexible enough to handle an increase in throughput, because cell clone, media and cell culture parameters can all be optimized to substantially increase the amount of protein.

One of the best examples is production of current influenza vaccines which is a cumbersome and antiquated egg-based production process. The egg-based method of vaccine production for flu vaccines for example is in place since the 1940s. It requires significant starting material, at least six months for production, and is extremely susceptible to contamination events. These inefficiencies can interrupt the supply of vaccines and heighten public vulnerability to disease. The change to a cell- or tissue-based culture system, begun as long ago as the 1980s, helps to mitigate several of these issues and ensure an adequate supply of vaccines. Growing vaccines in cell- and tissue-based systems alleviates the need for long lead time and can allow for better control and scale-up during manufacturing. Cell-based vaccines also have the added benefit of increased tolerability, as allergic reactions to egg components would no longer be an issue. For example, Novartis has shifted to cell-based vaccine and Abbott's acquisition of Solvay further signal the shift toward cell-based production systems. VaxInnate is also developing a cell culture-based *E. coli* bacterial system to produce influenza vaccine that is, currently, in trials.

The recent flu threat had caused the influenza market expanded rapidly. This growing commercial opportunity has encouraged companies to develop new technologies and increase manufacturing capacity for influenza vaccines and antivirals. The influenza sector has benefited from the increased disease awareness and funding due to the pandemic flu scare. Maintaining this market momentum in the coming years will be a major challenge, and it is likely that new technologies in manufacturing, adjuvants and delivery will drive

increased product differentiation in the flu vaccines market, and perhaps evolve it into a premium-priced area.

However, the high fixed cost associated with the manufacture of vaccines and long-term return on investment serve as major reasons why more companies have not ventured into manufacturing of vaccines. Thus, any initiatives towards developing new vaccine production methods must be driven toward a new approach in which vaccines are manufactured quickly, at a lower cost, and by more players globally.

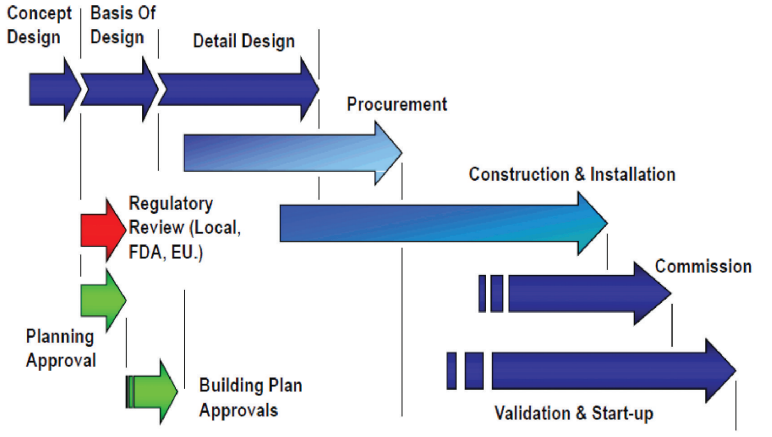

Figure 11 Process sequence to build a GMP manufacturing facility for biopharmaceuticals

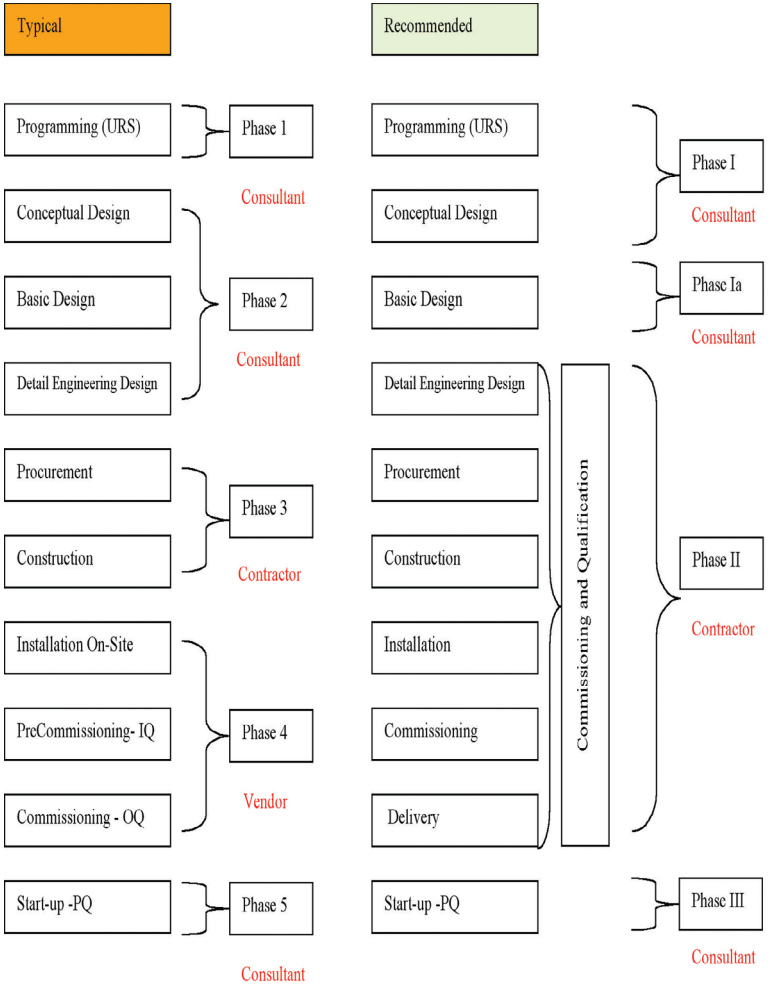

Figure 12 Typical Planning to build a pilot plant to produce biopharmaceutical bulks

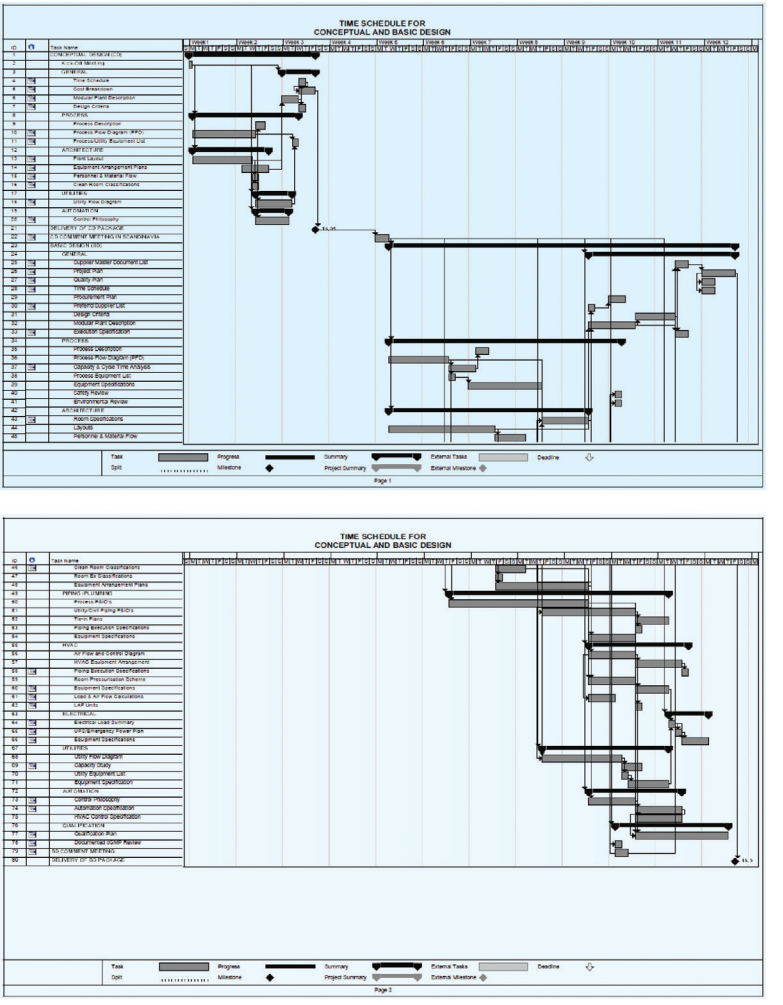

Figure 13 Typical timeline to building a pilot plant to produce biopharmaceutical bulks

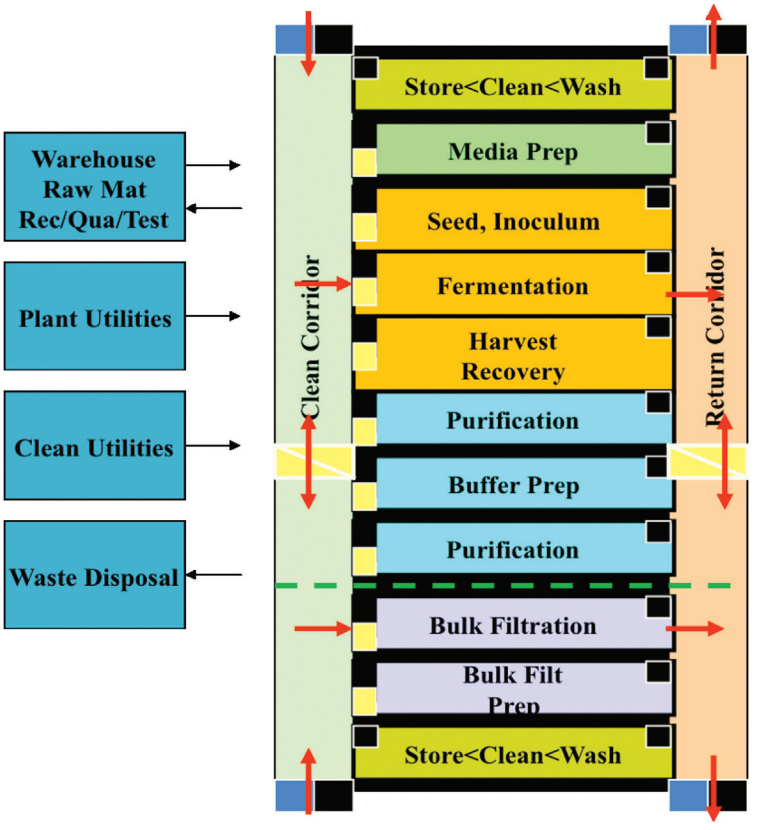

Figure 14 General concept of plant layout to produce biopharmaceutical bulks

Consolidation of Biopharmaceutical Industry

The driving forces behind consolidation of biopharmaceutical industry are due several factors. The cost of production will never go down. Thus it exerts cost-containment pressures particularly the larger pharmaceutical companies are facing growing costs from research & development and marketing. Furthermore, the global competition between traditional pharmaceutical companies is

accelerated by the changing economical realities of the healthcare systems world-wide. Next, increased complexity of clinical trials had caused clinical trials are becoming increasingly difficult to manage. The existence of global pharmaceutical giants demands simultaneous clinical trials in a number of countries. This in turn requires qualified personnel with abilities to organise the regulatory procedures and the development and maintenance of complicated information technology systems. Such an extensive infrastructure will result in high fixed costs that work against the cost-containment strategy. This has opened new possibilities for the dedicated outsourcing services. Thus, the most important factor for consolidation is increased versatility of outsourcing services. The areas most often outsourced are: 1) R&D, 2) clinical trials, 3) manufacturing and packaging, 4) marketing, 5) distribution, and 6) expert services (knowhow). The quality and availability of outsourcing services is important if the company neither capable nor willing to build and maintain all the required facilities of pharmaceutical product development and manufacture. For example, many of the small biotechnology firms have the facilities and expertise to produce gram amounts of biopharmaceuticals, but in the clinical trials the needed amount grows to kilogram range. This requires special manufacturing plants that meet the strict NRA requirements. The cost of building multipurpose GMP facility is RM70million (USD25million) to RM170 million (USD75million), and many biotechnology firms, with the risk of their new product not getting market approval are reluctant to finance a facility but rather are willing to outsource their production to contract manufacturers who are either dedicated service companies or firms selling excess capacity.

Reducing Time-To-Market

Contract manufacturing organization (CMO) approach

Increasing costs is one of major challenges confronting pharmaceutical and biotechnology companies. Thus, reducing time-to-market is an essential particularly when the end of patent protection is considered. One of the best option is to by partnership with a CMO that provides intelligent concepts and the proper experience, not only with respect to the production itself, but also with regulatory authorities. The time involved can also be significant. As many as twelve years can elapse between a discovery that seems to have therapeutic value and the approval of the new drug. The processes of discovery, development, testing, manufacturing and securing approval are demanding and require close cooperation among experienced partners Franklin's advice also speaks of the money lost when time is not used most effectively. Time is doubly important for drug development. Not only are the costs of testing and approval great, the entire economic profile of a potential drug also depends on time. Patents enable companies to recoup the costs of discovery and development, but the duration of a patent is limited; once it expires, the original manufacturer must compete with companies that have not had to pay for the costs of bringing a compound to market. Thus the incentives to have the longest possible period of patent protection are strong. The best way to lengthen that period is to move through the development and regulatory approval process – particularly the production and packaging processes – with the efficiency and speed that comes from working with an experienced manufacturing partner

Big pharmaceutical companies used to serve as contract manufacturing organizations (CMOs) as a last resort solely to achieve efficiencies in cost, capacity and time-to-market, or to

obtain a specific expertise not available in-house. Today, these factors still play a role, but the most dynamic driver behind the use of CMOs in the pharmaceutical industry is now the unique, innovative, and state-of-the-art process and production technology they offer. As a result, contracts between CMOs and pharma/ biotech companies are far more complex than take-or-pay and pay-for-service contracts of previous years. Companies are trying to establish a greater number of more involved partnerships in which there is a wider variety of terms and deliverables, creating stronger links between the organizations involved. Moreover, these sophisticated partnerships are not restricted to deals made between smaller players. Even the largest competitors are becoming more creative in their deal structures as they look to minimize costs and build greater operational flexibility. Biopharmaceutical manufacturing in particular has become a focus area for CMOs as the number of new biotechnology-based drugs moving rapidly out of development and through the final phases of clinical trials into full-scale production, continues to grow at a rate almost twice that of conventional drugs. Fast growth, however also brings its own inherent challenges which are principally technical in nature. In 2007, there were at least 400 monoclonal antibodies (mAbs) in preclinical development and more than 100 in Phase II clinical trials. One of the more optimistic forecasts for the mAbs market suggests that these products are set to account for one-third of all drugs on the market by 2010, making up around 60% of the pharmaceutical sector's revenue growth by that time. These highly engineered proteins are generally produced by mammalian cells and typically have far lower yields than, for example, recombinant bacterial systems that are used to produce many other types of biologics. Monoclonal antibodies generally have a shorter time to market and usually achieve higher success rates compared to small molecules.

These drugs also face reduced threat from generic competition as the regulatory situation regarding biosimilars is still unclear.

The are two most common models of CMOs: GMP manufacturers and those of the testing laboratories. Companies range from those that do only one of these to companies that provide the whole range of services. Even within each category, they tend to specialize around a particular set of skills and services they provide. GMP manufacturing requires large capital investments in equipment and facilities. In order to remain compliant with GMP operation, these facilities must be kept functioning at all times, which requires a constant feed of utilities and on-site support staff. This leads to a cost structure in which most of the costs, with the exception of raw materials, are fixed. CMOs tend to structure their fees to cover these fixed costs (plant amortization, utilities and personnel). Development and analytical support on the other hand tend to be priced as a fee for service. Since many different clients can be accommodated by a testing laboratory (unlike a manufacturing plant where only one client is present at a time), they make their money on the margin from running tests and price by the hour or by the test performed. When development is performed by a manufacturer in support of future manufacturing work, it is usually billed on a time and materials contract, though some manufacturers provide these services for a fixed fee.

Table 14 Services offered by CMOs

Service	Activity
Primary development	Pilot process development for active pharmaceutical ingredients. Production of preclinical batches and early-stage clinical manufacturing.
Custom primary production	Full-scale production of the bulk substance and its key intermediates.
Physical processing	Physical finishing or blending of a drug substance to facilitate its processing into a dosage form of drug delivery system.
Clinical lots manufacturing	Formulation of drug substance for clinical trials.
Formulation development	Production of a drug formulation based on standard technology or creation of an innovative drug delivery system.
Dosage form manufacturing	Production of a formulated drug in a form ready for final assembly and packaging.
Packaging	Final packaging and labeling for market. Formulations such as sterile products and injectible drugs require specific expertise.

Companies providing manufacturing services further differentiate themselves by the stage of clinical development for which they provide assistance, be it early clinical trial testing materials for phase I and phase II development or support of phase III and commercial sales. When new commercial approvals is slowing down, the market opportunity will be primarily in early development and outsourcing the manufacture of clinical-trial materials (CTM) is strong and growing. Demand for these services mainly stems from the increasing number of phase I candidates.

CMOs provide biopharmaceutical manufacturers the following advantages and flexibility:

- Providing manufacturers with immediate access to specialist technology platforms and knowledge bases not possessed in-house.
- Relieving strain during the launch of new products and when the market size is yet to be determined.
- Enabling manufacturers to 'switch-off' manufacturing, without cost or loss of staff, if a drug is failing.
- Enabling manufacturers to quickly manufacture products acquired through licensing and/or merger and acquisition activity.
- Providing assistance for registration and approval processes in foreign markets.
- Allowing manufacturers to increase the number of clinical trials underway, without a commensurate ramp-up in cost.

Engage an expert manufacturer to develop manufacturing scheme

CMO may provide the foundation for all of the manufacturer's projects. The manufacturer's team that completed development and

clinical testing should be involved in commercial manufacturing. This shall ensure the intimate knowledge of the compound and the filling process is retained when the challenges change from testing to commercial production. Continuity also avoids losing time on knowledge transfer from R&D to manufacturing team; should any difficulties arise, those involved will know the entire history of the project. CMO and representatives of commercial manufacturing shall review and evaluate product specifications and manufacturing requirements as well as technical options. For example, experienced manufacturing partners can often apply a process that has already been validated, shaving off even more time-to-market. In other cases, a new process must be designed, implemented and validated. In these situations, the development service's overall experience and continuity with the project will support efficiency and a shorter time to-market.

Ideally, once a project starts, a specialized manufacturing team begins to work with a team from the manufacturer to form a joint development team. The team defines steps, develops a checklist, including milestones to measure progress. The checklist to be compiled at this early stage will include all the equipment that needs to be ordered in time for the commercial production phase. CMO should be able to offer a solution that provides the manufacturer with the greatest convenience. At the same time, the solution should be one with which the manufacturer has considerable experience, as this experience can be brought to bear in increased process efficiency.

Integrated project management approach

The main factor in moving a project through development and testing efficiently is well-designed, integrated project management. This is to ensure all processes are synchronized so that they come together

at the earliest possible moment. For example, once a primary packaging system selected, the development team reviews the entire filling process – the filling machine, format parts and so on – so that it can begin informing the company's own suppliers who then, in turn, can deliver the necessary parts on time. The development team also studies the compound's particular characteristics and the packing materials to make sure they are suitable in terms of light-sensitivity, filling, pumps and other parameters. The checklist and milestones developed in the planning stage keep the process on track, shortening time-to-market.

Testing feasibility and production

With the preliminary plans in place and a detailed process roadmap drawn up, including testing and filling can begin. The first step is to perform a small-scale feasibility production activities e.g. filling. The small-scale filling shall be done manually and entirely under laboratory conditions. It constitutes a feasibility study that serves several purposes. Most importantly, it gives a quick indication of whether the approach is practical. These small-scale tests also determine the specifications of the product, including whether it should come in a single-dose or multi-dose packaging, what the fill volumes are and which storage conditions are necessary. One rule of thumb is that the more information the feasibility approach creates, the less time is required for adjustments during the commercial manufacture. Adjustments, changes or corrections can be performed in the laboratory much more simply than once it has gone into operation. Some companies have specialized knowledge of very sensitive substances that can bring concrete benefits in this phase of development. Whether the results of the feasibility study are applicable to big scale manufacturing must also be tested and validated prior to commercial manufacturing.

To scale up successfully, a number of steps have to be carefully evaluated and calibrated e.g. the thawing procedure of the bulk product, for example, and the definition of bulk handling and mixing properties. Filtration is another important aspect that requires expert knowledge. What kind of tubing will be used? What is the right tubing diameter? What is the maximum filtration pressure allowed? Experience in answering these questions makes the process efficient.

Final testing and initial manufacturing

Production of clinical batches begins as soon as scaleup success has been confirmed. To generate precise indicators for the master batch record, a minimum of three batches must be run, using a minimum of 10 % of the future commercial batch size. These batches can be used for registration purposes. The critical factors in determining their success are good manufacturing practices (GMPs), which are indispensable, the possibility of human use, which must always be borne in mind, and release of the batches by quality control and the qualified person. The runs testing the process' scaling up produce material for stability batches, which can also be used for clinical studies once the stability tests have produced positive results. In the aseptic filling process, each step in a project is geared towards greater safety and speed in the final stages. Prior to commercially manufacturing the drug, however, a detailed risk analysis must be performed for all steps of the process, followed by validation, which must be conducted on at least one full batch. All critical parameters are examined and tested. These include holding times, mixing properties and full-day production (robust processing). Simulating worst-case conditions is one way to cover all of these base values. Another is to validate an optional minimum and maximum batch size to build flexibility into the commercial production process. Validation also extends to various shipping aspects, including the

container, the packaging and the means of transportation. These tests and evaluations produce a validation protocol and report that are used for all future commercial batches, and these documents are to be submitted to the regulatory authorities.

One of the most effective areas for reducing time-to market for a new biopharmaceutical compound is packaging and all of the elements surrounding it. The processes involved in this phase are precisely planned, and valuable time can be saved. Working with an expert manufacturer that has the know-how, expertise, and infrastructure to implement the project efficiently can lead to significant gains for a drug development company. Experienced teams, integrated process management and active communication between all units and team members are crucial. Most important, however, is careful planning in the earliest stages to ensure that all steps in the process are recorded to save as much time as possible. An excellent track record with regulatory agencies such as the NPCB, TGA, FDA, EMEA and others means that companies can rely on the manufacturer's experience in maintaining the requested GMP status and navigating approval channels. The combination of detailed technical knowledge, close coordination with project partners and deep understanding of materials enables a good specialized manufacturer to help its partners improve efficiency throughout the development process, ultimately shortening the time it takes to bring a new product to market and improving the opportunities for sales.

INVESTOR'S PARADIGM

Fulfilling Unmet Needs of Healthcare

The market for pharmaceutical discovery companies can be divided into two parts: in the first market are the investors and potential

partners (may be large pharmaceutical companies) to whom a discovery company must market its profit potential and development projects, and those in the end market are the doctors and patients. These two markets are closely linked together. To succeed in the first market, issues on who will be paying for the end product must be solved first. The successful strategy here is to pay attention to the larger pharmaceutical firms that may have an interest in the product under development. These well-established firms have little need to trumpet their own research, and at the same time they are able to invest the resources needed to bring their products all the way to the market. To compete with a well-established full-spectrum company or a big pharma is quite difficult. The emphasis of unmet needs as a key success factor is required strongly by many potential investors. Gaining global visibility and credibility is easier when a company targets a very specialized sector with clearly unmet needs.

Strong Technology Platform

A high-quality new product process is one of the strongest common features of high-performance businesses. It is somewhat difficult to differentiate the impact of the number of products in the pipeline from the strong platform: the novelty and quality of the platform (patents, technologies) are essential to keep the product pipeline saturated. It is the innovativeness and therapeutic superiority of products that attracts investments to the company. A strong platform was understood to constitute possession of wide immaterial rights. The importance of a strong platform in the modern virtual business structure was stressed by experts. Despite failure to launch its final products, companies with a broad IP portfolio will have still a great potential to create new value from new application of their IP.

First to Invent First to Market

Another key factor for a successful company's products is marketing. Again, there are two target groups: the first market (big pharmaceutical companies and venture capitals, VCs) and the end users of the drugs (doctors and patients). It may even be that the product must be marketed to insurance companies, opinion leaders, and public health agencies. Planning rapid market penetration is essential to any company's success. Marketing should begin early in the product development cycle, and there are a few questions to be asked: First, how will the product be positioned in the market? This should be expressed in terms of product value and use, and it should be borne in mind that the end-product customers are primarily doctors and medical personnel. Second, how will the product be distributed and sold in both domestic and foreign markets? The strategy of the majority of small firms is to form alliances with larger pharmaceutical companies, but as companies mature and grow their product portfolio, their own sales channels should be evaluated. In the interviews marketing of the company as a whole was often brought up. The analysis of market positioning and profile of the products in every phase of the development must be considered as a success factor. The entire product development process shall also be considered as the initial phase of marketing. A relationship with the potential partners must be built early on "to get people interested in what the company is doing" as part of a successful product strategy.

Figure 15 The pharmaceutical value chain for new innovations. Marketing is considered as the biggest proportion of the final value to the stakeholder.

Licensing

Licensing deals are a popular way for pharmaceutical companies to access emerging, high potential drug candidates. Deals may be completed in relatively short order, after a review of the technology has demonstrated a potential fit between the goals of the investor and developer. Although rising competition for leading biotech drug candidates has pushed deal value up and resulted in relatively large upfront payments, these nonetheless are usually considerably lower than payments made as project milestones are reached. This allows termination of the collaboration if and when expected progress is not achieved; in practice, project termination is not at all uncommon, for licensing agreements that were entered into when drug candidates were in a very early stage of development as well for later-stage compounds.

Most licensing agreements now have “no-fault” termination clauses that may be exercised by the partner upon 60 or 90 days notice. Typically, the investor’s role revolves around financial backing of the drug during its development stages; the investor may also assume responsibility for regulatory filings as well as marketing and distribution once the drug/s is approved. The developer usually conducts the hands-on development of products, especially for early-stage development deals. This is beginning to change, however, with some investors playing a greater technical role in the development process. Licensing deals work particularly

well when one party has unique soft assets (such as intellectual property and scientific know-how) but does not have significant hard assets (employees and facility) that could be rationalized in an acquisition to extract value. They may be entered into at any time during the drug development process, but are most common in later stages once a technology has been validated.

The biopharmaceutical business deals are usually licensing agreements in which the licensor has a vested interest in seeing the licensee succeed in financial and marketing sense. As to the terms of payment itself there are no internationally unified systems in existence. Even the terminology used is different depending not only on the country in question but also on the nature of the business deal. However, one can distinguish between the four most usual payment methods which are: 1) preliminary or initial payment, 2) down payment and annual royalty, 3) annual royalty, and 4) milestone payments.

1) *Preliminary or initial payment*. Preliminary payments are compensations made before signing of the agreement for the costs caused by, for example, a feasibility study, documentation or the development of the licensing offer.

2) *Down payment and annual royalty*. In this payment method, the licensor wishes to gain a sum of money in advance, and an annual royalty based on some clause, e.g., level of sales or period of time. The larger the initial down payment, the smaller the on-going royalty rate.

3) *Annual royalty*. This is merely an annual royalty payment without an initial down payment.

4) *Milestone payment*. This is not exactly a payment term used in the licensing agreements but rather an investment to a project, which is done by someone else. For example, an established

pharmaceutical enterprise could finance the drug research process of a biopharmaceutical firm under the agreement that the resulting product is licensed to the established pharmaceutical enterprise.

Successful Technology Transfer

Why biotech technology transfer deals fail

Many biotech tech transfers fail to meet the expectations of one or both parties.

- Project failure can include inability to meet goals on time, failure to meet goals on budget, total inability to meet one or more key scientific goals under any circumstances, inability to meet one or more key business goals, dissolution of the alliance prior to previously agreed termination date and/or legal recourse by one or both parties against the other.
- The failure of a biotech technology transfer can have significant implications for both the technology developer and the investor, although consequences are usually more serious for the developer due to its often smaller size and greater reliance upon a single revenue stream.
- In contrast, most technology investors have projects in many different areas and are not reliant upon a single application or approach.
- However, because technology investors tend to seek out and acquire large numbers of new technologies on a regular basis, large numbers of deal failures can, in the aggregate, impact their competitiveness.
- There are many reasons why biotech tech transfers fail including failure to conduct appropriate due diligence, establishment of

an inappropriate deal structure, management changes at the investor, cultural differences between the partners, project organization and differing expectations and technology failure.

- While many factors can influence the success of biotech tech transfers, analysis of large numbers of such relationships has shown that manner of partner introduction and location of partners.

Strategies to ensure successful biotech technology transfer deals

- For both developer and investor, a successful tech transfer means, at a minimum, that the agreement terms have been fully satisfied and the contract has been fulfilled without early termination or penalty.
- Depending upon the scope of the contract, however, both groups often have additional criteria constituting relationship success.
- With a large and rising number of biotech tech transfer agreements each year, both technology developers and investors have developed strategies to increase the probability of success.
- Strategies to increase biotech tech transfer success for both technology developers and investors include tools and approaches that address issues of interest to both parties, such as techniques that meet technology challenges.
- Strategies for biotech technology developers to help ensure tech transfer success address the unique challenges faced by these groups, including techniques to optimize resources, think like a customer, work with professional technology transfer organizations and publish prolifically.
- As many biotechnology investors are larger enterprises with extensive drug development programs that span a broad range of

applications, a large proportion have established sophisticated processes to identify, consummate and manage appropriate tech transfer relationships.

- Over the years, these biotech investors have developed best practices that address key aspects of relationship success, including technology identification and due diligence, structuring innovative deal terms, addressing compensation issues, fostering an entrepreneurial technology developer environment, ensuring effective alliance management, navigating cultural chasms and addressing international intellectual property challenges.

The future of biotech tech transfer deals

- Over the next five years, the role of biotechnology in drug development is expected to expand strongly as biotech drug sales rise by 17.7% per year while small molecule drug sales grow by just 2.9% annually.
- Through 2015, pharmaceutical companies will continue to embrace biotechnology, although this trend will be more significant for some companies than for others. Growth will be driven by increasing drug development difficulties, ongoing patent expirations and international competition.
- However, the very high prior rate of biotech tech transfer deal value growth is expected to decline from 27.1% per year to 18.5% per year as technology valuations become more closely aligned with actual market potential.
- Biotech tech transfer deal volume is expected to continue to expand at a moderate pace of about 5% per year; growth will be supported by a proliferation of new technologies

related to gene therapy but constrained by an ongoing lack of commercialization resources, particularly at universities and other research institutes.

- Licensing will remain the most desirable form of technology ownership for tech transfer investors as a relatively weak economic environment makes companies less willing to engage in risky acquisitions and joint ventures.

Funding Issues

Funding for biotech companies is derived from several key sources, to include: direct investment from original founders or promoters, in which funding is exchanged for company equity; venture capital, a more structured process of exchanging funds for company equity; and initial public offerings (IPOs), in which company equity is offered to the public through a normal offering of shares on a public exchange. In recent years, and particularly following the recession of 2008 and 2009, each of these funding sources has decreased considerably, resulting in a shortfall of funding available for biotech R&D worldwide. In the UK for example, 78% of respondents found that access to capital had become more challenging in the past year, 76% of those seeking to raise equity financing experienced difficulty and of these, 37% were unable to obtain any funding. While direct investment includes funding provided by smaller investors ("friends and family"), it mainly comprises larger tranches supplied by professional investors such as mutual funds. In the US, these investors typically include specialist healthcare funds that understand the drug development industry and are prepared to commit greater resources for longer periods of time; in Europe, however, they tend to include more generalist mid-cap investors who are less well acquainted with the uncertainties of

the drug development business. Both types of investors, however, have been impacted by the steep decline of global stock markets in which equities lost one third of their value between late 2007 and early 2009.

Biotech companies have also seen decreased venture capital funding. Venture capital funding of US companies declined substantially in 2009 compared to prior years, with total funding ranging from just $3.3billion to $5.0billionn per quarter, compared with $7.4billion to $8.2billionn per quarter in 2007. While the biotech sector remained the second highest recipient of venture funding after software, receiving $905m to $1.2billion per quarter in 2009, this nonetheless represents a substantial decline from prior years, when the US stock market was high and the prospect of successful initial public offerings (IPOs) for high potential biotechnology companies was an attractive draw for investors. However, total IPO volume is down sharply, with just 15 US IPOs of venture-backed firms in 2008 and 2009 combined, according to the National Venture Capital Association (NVCA); this compares with 86 such deals in 2007, 57 deals in 2006, another 57 deals in 2005 and 94 deals in 2004. Even these levels, however, represent a significant decline from years past, with more than 250 IPOs in 1999 and 2000.

Table 15 Capital raised within the 12 months (2008/2009) by type of enterprise in Europe

	None/no capital	€<1m	€1 - 4.9m	€5-10m	€>10m	Do not know/no answer	Total
	Number of enterprises						
Platform	0	4	1	1	0	0	6
Pre-clinical	1	16	13	1	1	1	33
Clinical phase 1	1	1	3	2	0	1	8
Clinical phase 2	2	5	6	3	3	1	20
Later-stage	0	2	1	1	4	0	8
Product(s) on market	2	1	3	3	3	0	12
Total	6	29	27	11	11	3	87

Source: DTI-biopharmaceutical survey in Europe, May June 2009

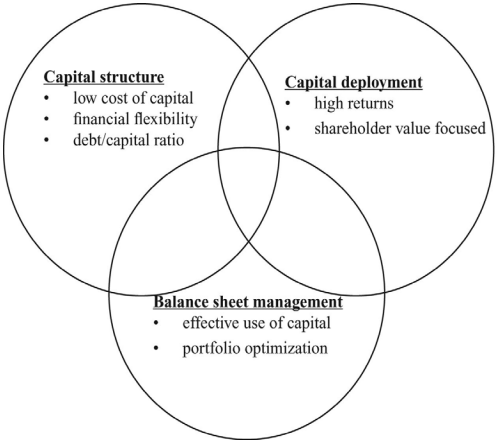

Figure 16 Value-focused financial strategy: driving high growth and high returns

ENTREPRENEURSHIP IN BIOPHARMACEUTICAL

Entrepreneurship Characteristics

Entrepreneurism is a characteristic difficult to define. In a sense, commitment, team-work, and management skills could be understood to be characteristics of entrepreneurism. Entrepreneurial personnel must be individuals who can succeed in different environments, show tenacity, have a sense of urgency, and who are pragmatic and can identify the non-obvious. Every scientist who joins a biotech company should realize the fact that it is not all about the excitement of science and technology, but about sustaining a profitable business and moving forward. Most scientists from academia might not agree with this reality as they are not aware that their R&D is only a small part of the big value chain and funding obtained for their research must be justified towards unified objective of value creation. The desired quality of entrepreneurial characteristics for biopharmaceutical companies is people who are generalists, who are able to do many things (on whatever it takes), drivers and they must have the ability to maintain enthusiasm and speed in business development.

Management Team

The importance of financial and managerial viability of the developer organization cannot be over emphasized in the case of tech transfers that will involve an ongoing working relationship since the ramifications of avoiding this part of the due diligence process can be severe, and include a financial "bailout" from the investor should the developer organization not have sufficient funding in place. In the worst cases, such relationships will become impossible if the developer group simply ceases to exist due to a lack of funding or over-reliance on one particular deal. For

example, Anevisa filed for bankruptcy in early 2010 after a planned merger with Arcion Therapeutics was terminated; the merger had included provisions requiring payback of funds from a stock sale and the retirement of certain debt. Many technology investors, therefore, request financial documents and other materials during a formal audit to determine the developer's ability to maintain its ongoing operations over the length of time covered by the tech transfer relationship. An audit does not always identify financial shortcomings, however, as Hawaii Biotech had not reported any financial weakness prior to its December 2009 bankruptcy filing.

Managerial strength can be even more difficult to determine. Some investors request personnel files and/or interview developer staff in order to ascertain employees' likelihood of remaining with the company; this is particularly important when scientific or technical expertise resides with just a few key individuals. Some developer organizations demonstrate clear managerial strength. For example, Genzyme continues to be named a top employer in a global survey ranking the reputations of biotech and pharmaceutical companies. In 2009, Genzyme ranked third on the list of 575 companies, the second consecutive year it has achieved this position. Genzyme placed among the top 10 of all biotechnology and pharmaceutical companies in the world for the seventh year in a row. The survey, which was commissioned by *Science* magazine and the American Association for the Advancement of Science (AAAS), identifies the top 20 companies with the best reputations as employers and includes the opinions of more than 2,300 respondents. Such measures clearly suggest strong managerial practices and mitigate risks related to high turnover,

Management change at biotech companies is not viewed by investors as a substantial cause of alliance failure. This is likely due to the fact that many biopharmaceutical companies are run by their

founders, who often invest many years into developing the company and technology; as well as the relatively few areas in which most biotechs work. Consequently, relationships with investors are treated by most biopharmaceutical companies with the utmost care and concern, so that biotech management changes, when they do occur, tend not to have a significant impact upon relationships already in place. On the other hand, one of the most frequently cited causes of alliance failure by biopharmaceutical companies is a change in senior management at the investing company. Because such changes are often accompanied by a shift in the investor's research priorities, a senior management change can impact the day to day workings of an alliance in many different ways that include a:

- Change in the scientific and business staff at the investing company responsible for the alliance;
- Corresponding shift in project expectations and/or workflows;
- Reassessment of the biotech partner's contribution, leading to a reconfiguration of each partner's roles and responsibilities;
- Reduction and/or substitution of resources allocated by the investor to the alliance;
- Change in cultural climate, affecting the ability of alliance workers to effectively communicate with each other and with partner staff;
- Diminished interest in the alliance on the part of the investors, even leading to a premature termination of the relationship.

Management changes in the pharmaceutical industry have been occurring at a brisk pace as a result of ongoing industry consolidation and downsizing. Management changes in investor

management can cause changes in the investee company as new executives tend to enter new positions with their own project priorities. Many equally worthy projects often compete for limited company resources and incoming executives may not have a full understanding, and therefore appreciation, of the alliances entered into by their predecessors. This is particularly true for global pharmaceutical companies, which maintain development activities in many different areas, working with dozens of partners in various capacities. Biopharmaceutical companies are also contacted on an ongoing basis by hundreds of biotech companies seeking to enter into relationships with them, and often have their pick of partners.

Challenges and Opportunities in R&D

Similar to any other biotech companies, biopharmaceutical technology developers rely heavily upon external funding to continue their operations. They need to develop or acquire new technologies to enhance their efficiency and competitiveness. All biopharmaceutical developer suffered from an ongoing conflux of factors that complicated the R&D process to include more complicated and increasingly interconnected disease targets; escalating research costs; increased regulatory scrutiny and demand for more clinical data; and fewer in-house R&D resources. Biopharmaceutical companies often have no saleable products to generate cash that will fuel operations, then they must rely on investor funding. With ever lower levels of such funding available, many are now turning to technology transfer arrangements to fund continued operations. In fact, while many biopharmaceutical companies initially tried to become fully integrated drug-makers, with capabilities spanning the full range of a drug's lifecycle (R&D, manufacturing and sales), this goal for many has proven impossible to achieve as the odds of successfully launching an independently

marketed therapeutic product proved far lower than expected. As this occurred, many of these firms switched gears to become research houses and now fund their R&D operations from equity capital and the proceeds of alliances with pharmaceutical or larger biotechnology companies.

As biotechnology has emerged as a highly successful new approach to drug design, technologies have proliferated but most have not been fully exploited. While few of these discarded technologies represent significant breakthroughs, many offer incremental improvements whose inventors were unable to follow through with development due to resource constraints and other practical problems. This has given rise to an industry of brokers or consultant who act as middlemen between biotechnology developers and investors, arranging transfer deals. These brokers, who may act on behalf of either the technology developer or investor, take many different forms and often play several roles; they include:

- University or other research institute technology transfer offices;
- Licensing professionals at biotech and pharmaceutical companies;
- Independent consultants who take a fee from technology investors upon deal completion;
- Technology financiers, such as venture capital funds, who act as matchmakers for their investees.

The degree to which each type of broker actively pursues tech transfer opportunities varies; some are extremely aggressive and actively pursue a large number of opportunities. Others are more selective. All benefit from a heightened interest among

both technology developers and investors in tech transfer and a proliferation of new information and networking tools that enable this process. These include detailed reports and databases that are regularly updated with technology and deal information, industry events that bring developers and investors together, and interactive tools that permit ever greater levels of information sharing. Brokers bring many benefits to the tech transfer process. Importantly, they often initiate deals among parties that would otherwise not meet. During the subsequent evaluation period, they also maintain deal momentum by:

- Providing technology, business and other information to the developer and/or investor;
- Maintaining communications between technology developer and investor;
- Assisting in negotiations and/or deal structure;
- Identifying commercial opportunities for a technology.

The first three roles not only keep the deal moving but also help build the relationship between technology developer and investor; this is particularly important when the two parties will work together after deal signing. The last role, while not common, can nonetheless be critical as many technologies require other enabling technologies in order to be useful. In gene therapy, for example, a complete approach might include a particular cell line, a specific vector and corresponding gene vectors, each of which might be licensed from different developers. By virtue of their broader vision, broker is often able to put together these pieces when a single inventor cannot.

Due Diligence Failures

Due diligence is the process by which an investor investigates a technology and its developer to determine whether or not a relationship is appropriate. Even in circumstances involving competitive bidding and/or time sensitivity, it is generally considered that the more thorough the due diligence process, the better, as this is the primary means by which a investor can fully evaluate a technology. Key factors to consider include, but are not limited to:

- Ability of the technology to perform as desired ;
- Demonstrated successes of the technology;
- Ability of the technology to perform consistently;
- Existence of other technology investors and their experiences with the technology and its developer;
- Patent issues;
- Ability of the technology to meet investor needs;
- Expertise within the investor organization to work with the technology;
- Resources within the developer organization to provide investor assistance;
- Financial and managerial strength of the developer organization;
- Any roadblocks to the ability of both organizations to work together.

Where shortfalls in any of these areas are found, they should be thoroughly vetted so that the investor has a clear understanding

of the strengths, weakness and potential pitfalls of the technology and relationship with its developer. This may involve not only many meetings between scientific and managerial personnel, but also a significant amount of background work to check the validity of the technology in the context of its prior usage and the investor's own needs. While this can be time consuming, the rewards can be great, as thorough due diligence can prevent many serious downstream problems including overestimation of market value of technology; low commitment on the part of the technology developer to the relationship, incompatible objectives and selection of the wrong partner.

Unfortunately, many biotech tech transfer investors do not invest sufficient time or resources in this process to fully understand the scope of the technology and the relationship with its developer. Instead, much of the was spent discussing monetary terms and/or exclusivity while diligence requirements were much less rigorous.

Patent Issues

Patent issues are also critically important, since a lack of patent protection for technologies under development could instantly remove any gains from technology development. In this regard, the two items of most concern to a tech transfer investor are:

- Solid and comprehensive patent protection for any technologies or products already developed by the partner, which would be jointly used or developed;
- An agreement regarding ownership of any intellectual property arising from the development of additional technologies or products during the partnership.

Most university have sufficient legal resources to address both of these issues. When working with university-based technologies, therefore, technology transfer investors can usually expect that patents have been issued or applied for; in cases of early stage and/or quickly emerging technologies, legal resources are usually made available to address these issues once a investor indicates interest.

Start-up companies and other groups, however, often do not have easy access to patent attorneys and other legal expertise. In these cases, the investing company may have to verify the patentability of the invention on its own in order to ensure that the technology is, in fact, proprietary. This is also a necessary step in determining deal value, since a technology that is not proprietary – or infringes on another patent - cannot command the same price tag as a technology that is truly unique.

Deal Structure

The structure of a biotech tech transfer agreement typically involves several key terms including payments, exclusivity, termination clauses and responsibilities. This last item is particularly important where the developer and investor will have an ongoing relationship and in fact, the most successful biotech tech transfers tend to be those in which relationships between technology developers and investors are well defined from the outset. This includes a clear written agreement between the parties that delineates all items of interest such as compensation, intellectual property ownership, areas in which the investor may utilize the technology and/or exclusivity, ability of the investor to sub-license the technology, warranties and contingencies for termination. A well-written contract is particularly important when the arrangement will feature an ongoing working relationship between the parties. In this case, it should specifically include, in addition to the items above:

- Pay and rewards linked to performance of the technology and/or the developer;
- Early establishment of a small and consistent core team including key players at the developer and investor;
- Clear division of responsibilities between the technology developer and investor. Although the investor's overarching R&D goals may be quite broad, including, for example, the introduction of new clinical candidates, additional drug approvals, etc., technology performance as determined via due diligence and defined by the contract is usually limited to certain very specific and well-defined objectives related to the unique capabilities of the technology itself.

It should also be noted that in many cases, the technology investor has considerably more input into the development of the contract and often writes the agreement. In these cases, the developer may feel compelled to accept terms that are not as favourable as it would like, leading to potential fulfilment discrepancies as project work starts. Ideally, both technology developer and investor should remain cognizant of these issues and develop an agreement that delineates attainable roles and responsibilities for both parties; however, this is not always the case, especially when an eager technology developer needs funding for ongoing operations. The less common exception to this is "hot" technologies with multiple suitors; in these cases, the developer may find that it has the upper hand in negotiations and may even benefit from bidding wars among competitors.

Opportunities and Challenges in Emerging Markets

Healthcare opportunities include:

- Diversification opportunities outside of big biopharma markets (i.e.,. US, Europe and Japan)
- Access to large and varied populations;
- Access to worldwide talent and science;
- Economies of scale for return on investment;
- Increasing and earlier detection of diseases;
- High rates of infectious disease, "developing world" diseases, HIV/AIDS and hepatitis;
- Respiratory diseases due to high rates of smoking, pollution, and industrialization;
- Large pediatrics markets in countries with high birth rates;
- Increasing rates of chronic diseases including hypertension and diabetes with longer lifespans.

The opportunities presented by the emerging markets are numerous:

- Large populations;
- High unmet medical need;
- Population growth;
- Growing economies;
- Increasing public and private healthcare expenditures;
- Increasing philanthropic funds;

- Lower labour costs;

The challenges presented by the emerging markets are also numerous and include:

- Diversity of languages and cultures;
- Patent law/intellectual property protection;
- Diverse healthcare structures and policy;
- Distribution logistics;
- Talent pool/education/literacy rates;
- Political environment and stability;
- Country or healthcare infrastructure;
- Foreign exchange risk;
- Security issues;
- Complexity of Human Resource and labor issues;
- Pricing regulations and controls;
- Local regulations, taxes and tariffs, and
- Preferential treatment for domestic companies.

Value Creation Via Merger & Acquisition (M&A)

M&A deals among biopharmaceutical companies are likely to gain in popularity as more companies look to generate growth from biological products. Expanding product portfolios and gaining access to technology will continue to be the main drivers of acquisitions. Biopharmaceutical companies are forecast to be

the most active acquirers of biopharmaceutical concerns, with inter-company deals accounting for a smaller but substantial share. Competition for late-stage candidates will shift the focus to earlier-stage product deals as biosimilars gain market approval. Biopharmaceutical companies that build their business through acquiring a broad product range and wide geographical market spread will be favourably positioned to attract new investment and future alliances. These companies will in turn be potential targets for big-league pharmaceutical companies.

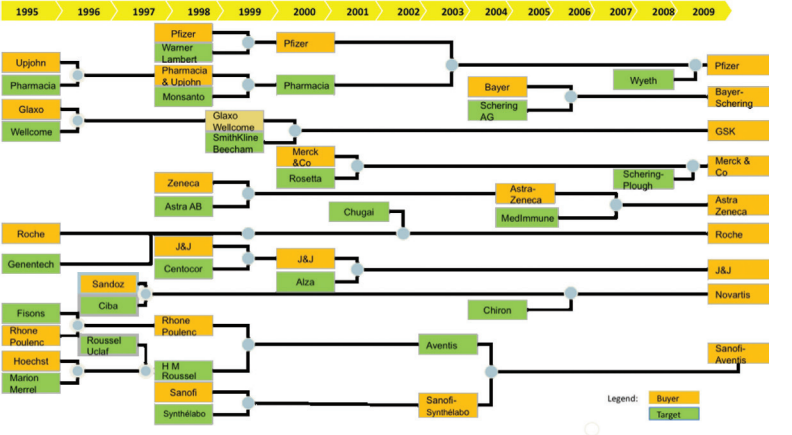

Figure 17 M&A and leading pharmaceutical companies

CONCLUSION

Efforts to develop therapeutic proteins, vaccines and other biologics that will change the lives of the many are, for human or animal use, getting more challenging, costly and risky. Certainly, the disease areas represent high unmet medical need and it has proved challenging to find effective therapies. Whilst the development of biopharmaceuticals provides a unique opportunity for successful

therapies in these areas, the technical hurdles to approval and launch a new product can be high. The disease may not be well understood and the clinical pathways to approval are often untested. Technology transfer is becoming an important way for biopharmaceutical developers to access new approaches to increase R&D productivity and output. Meanwhile, expectations for new drugs from regulatory agencies, from patients and from payers are getting higher. Regulatory agencies are rightly focused on patient safety and risk management more than ever before. It is not enough to demonstrate that a medicine is safe and effective – drug developers must also demonstrate that it adds value to payers and is a significant improvement upon existing therapies. This means that the time to develop new medicines is getting longer and costs are increasing. There will also be increasing pressure on pricing and cost of goods as biologics progress into therapy areas where much cheaper medicines are already available. So what will make biopharmaceutical and biotech companies successful in developing new medicines over the next decade? Certainly, scientific and operational excellence coupled with a global focus will be the key. Re-structuring to ensure optimal use of resources and to ensure nimble decision-making is occurring across the industry. Most biopharmaceutical companies are looking to optimize their processes to reduce cycle time and increase the probability of success. However, it is ultimately right human resource that will make the difference. Outstanding leadership, recruiting and retaining key talent and fostering an environment that allows creativity and managed risk-taking to flourish will distinguish the new biopharmaceutical and biotech giants, and that is the way forwards to address the issue on twists and turns post-genomic area.

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BIOGRAPHY

Mohd Azmi Mohd Lila, aged 46, since 1990 and currently is with Department of Pathology and Microbiology, Faculty of Veterinary Medicine, Universiti Putra Malaysia. He has many years of experience serving various aspects of life sciences and biotechnology especially in research and development (R&D), product and technology innovations, technology acquisitions and investments, entrepreneurship, commercialisation of IPs and technology management. He has been engaged as a consultant and advisor by many companies and served as a committee member of various private and government institutions and authorities including Khazanah Nasional Berhad, Ministry of Human Resource for recruitment of human resource for emerging industry in Malaysia, committee member of Self-reliance Vaccine Production Program (by Islamic Development Bank, OIC), and Malaysian Debt Venture for setting up of RM1.4 billion debt venture fund.

He was also the chief executive officer and executive director of Ninebio Sdn Bhd (2009-2011), a government owned company (GLC) focused in research and development, commercialisation, manufacturing and distribution of vaccines, biologics and natural products. Ninebio provides supporting services related to manufacturing and HALAL certification activities to multinational companies to include Merck, GlaxoSmithKine and Novartis. He was responsible for the strategic direction, business development and overall management of the company. Throughout his tenure, he managed to restructure the company to ensure the right business direction, right funding requirement, financing and to ensure good governance/compliance in place.

Prior the secondment to Ninebio, he was the Director & Head of Investment at the Malaysian Technological Development Corporation (MTDC) (2006-2008), a Government owned venture

capital company and also handling government grant funding aiming to spearhead commercialisation and the development of technology-driven businesses in Malaysia. During his tenure there, he was responsible in managing the investment portfolio of few hundred million ringgits. His key areas of responsibilities include deal sourcing, evaluation of companies and business proposals, monitoring of investment and investee companies as well as corporate finance activities including deal structuring, management buy-outs (MBO) and fund raising. Throughout the process, he has reviewed extensive numbers of business plans and visited hundreds of business establishment for investment decision purposes. Dr. Mohd Azmi served as a BOD member of various investee companies in Malaysian abroad; and some of these companies are now on the path towards public listing. He was also responsible for the establishment of Malaysian Life Science Capital Fund, USD150million, a joint venture company Malaysia-USA) and also as a member of Investment Committee. The nature of business of investee companies under him ranging from R&D to manufacturing of life sciences products, vaccines and pharmaceuticals, healthcare products, fertilizers, minerals, chemicals, waste management & recycling, bio-diesel and bio-fuel (upstream development and engineering), biomedical devices/equipment, electronics, energy conservation and carbon-credit (CDM) related companies. Dr Mohd Azmi was also an exco member and the Honorary Secretary of Malaysian Venture Capital Association (MVCA). MVCA oversees programs and activities of venture capital and private equity investment companies in Malaysia.

He used to serve as a Director to public listed companies including TDM Berhad (plantation & healthcare sectors) and INS Bioscience Berhad (natural products & marketing).

He was the Director of the University Business Centre (2001-2002) and the Director of Institute of Bioscience (2004-2006). He has contributed and collaborated with many researchers in various research works and had his works published in various journals and publications (more than 250 publications). He managed to secure large amount of research funding from the government and private sector for R&D and acquisition of technology. He has supervised about 50 post postgraduates and at least 35 of them have graduated with MSc and/or PhD. He has numbers patented/patent pending invention and won many awards/international recognitions for his research and achievements, and to name a few: Geneva gold award, MAMPU innovation award, The Outstanding Young Malaysia Award, UMNO Melayu Cemerlang Award, PESAT (Terengganu) Award, and Outstanding Research Award (UPM).

Dr Mohd Azmi was born in 1964 in Chabang Tiga (Kuala Terengganu); primary school Sekolah Rendah Kebangsaan Pusat Chabang Tiga (1971-76); secondary school Sekolah Menengah Sultan Ahmad, Kuala Terengganu (1977-1981), received his first degree DVM from the Universiti Putra Malaysia (UPM, 1983/88) and PhD in Virology/Immunology from the University of Cambridge (UK) (1991/1994). He also holds MBA in Finance/Marketing from the UPM (1996/2000) and Masters of Law (Business Law) from the International Islamic University Malaysia (IIUM) (2006/2007).

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