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INTRODUCTION AND HISTORICAL PERSPECTIVE

1.1. BIOTECHNOLOGY : AN INTRODUCTION

Occasional developments in basic and biosciences lead our knowledge to be much more application oriented with great potential for further innovation. The developments which revolutionized 'biosciences' could be sporadic but certainly imparted great wealth to the more specialized discipline; referred to as **biotechnology**. The domain of biotechnology thus integrates most modern and highly specific technologies on one hand and traditional fermentation processes which our ancestors developed and practiced thousands of years ago, on the other. The use of fermentation technology in the preparation of medicinal agents can well be traced long back especially in the Indian system of medicine 'The Ayurveda' particularly has ever been engaged in the utilization of the fermented products as medicaments. However, the interest in the subject has been generated in the last few decades. Before going into an in-depth study of the subject it is necessary to know its evolution.

Biology is the science of living creatures. There is a great diversity in life starting from the simplest virus to the complex human being. But the basis of all organisms is the tendency towards organization leading to diverse forms. So the similarity between a man and bacteria is at the cellular level only. Further understanding of chemistry throws light on the atoms and molecules which are basically the same in the living and non living, just differing in the type and diversity of organization. Attempts have been made to postulate the theory of life using some fundamentals of biological and chemical sciences leading to the subject called **Biosciences**. Fundamental Biosciences account for the relationship between life and matter either through vitalism (that life is made possible by some force that is neither chemical nor physical) or mechanism (that life can be explained entirely in chemical or physical terms). However, the study is fast leading to newer conclusions.

Fundamental biosciences deal with the study of living systems in a wider perspective (Fig.1.1). Enormous research and the newer information drawn there from have led to revolutionary developments in the field of

industrial and applied biosciences. It has led newer perspectives of biology (growing with a multitude) and an increase in scientific knowledge. This knowledge of biological sciences offered to better industrial and therapeutic success and has been referred to as **applied biosciences**. This is the area where man has over powered other biological communities for a better living.

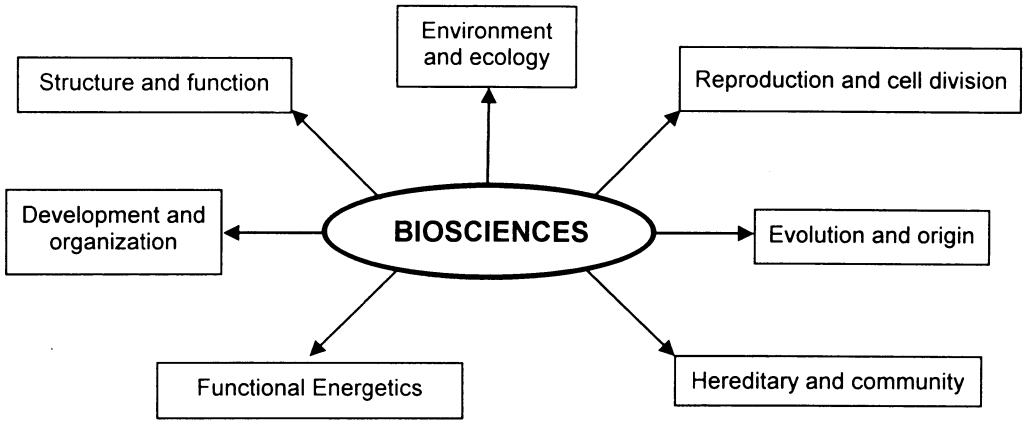

Fig. 1.1 : Biosciences a wider field and perspective

Applied biosciences cover the aspect of production and detection of newer therapeutics viz., antibiotics, peptides, better agricultural science, conservation of living resources, etc. (Fig.1.2). Therefore it could be said that fundamental biosciences have been developed to form applied biosciences for better living and building a good economic status.

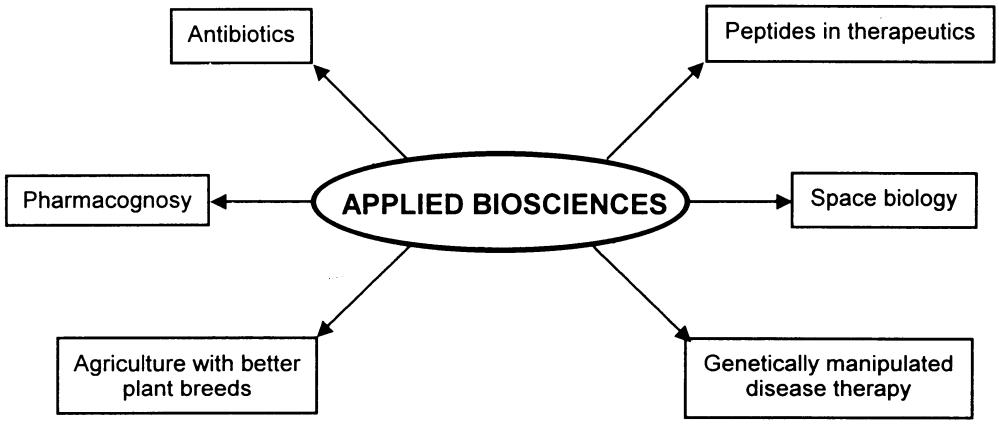

Fig. 1.2 : Applied biosciences in building a newer status of life

With advances in biosciences particularly in the fields of microbiology, molecular biology and biochemistry utilizing better instrumental facilities, a newer branch of biology has emerged as ***Biotechnology***. It is referred to as a link between the biological (life) sciences, physical sciences, chemical sciences and technological achievement, commonly referred to as the '*clever*' science of biology. The word biotechnology was coined in mid 1970's as a mixture of '***biological technology***' so as to differentiate from biomedical engineering and biochemical engineering. One of the most recently quoted definitions of biotechnology is "*the application of scientific and engineering principles to the process of materials by biological agents to provide better goods*

and services". But the terminology looks a bit vague. Another frequently quoted definition of biotechnology is *"the application of biological organisms, systems and processes for manufacturing and service industry"*. Still all aspects of the subjects are not clarified. Hence, biotechnology could be represented as a mixture of various biological sciences for better services in field of medicine and agriculture (Fig.1.3). Biotechnology has been identified and experimented upon as a science of techniques which makes use of biological systems interalia. In a real sense it could be presented as an alloy of many disciplines influenced by various parental sciences.

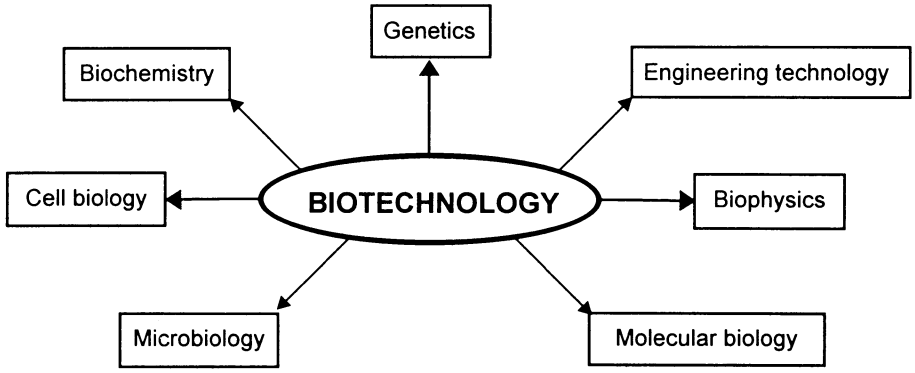

Fig. 1.3 : Various basic biological disciplines involved in the origin of biotechnology

The advances in the field of biotechnology have altogether influenced many fields of applied sciences. This has led to the introduction of many branches of biotechnology as agriculture biotechnology, medical biotechnology, engineering biotechnology, pharmaceutical biotechnology, textile biotechnology, paper biotechnology etc. Each of these branches could be defined as follows:

Agriculture biotechnology: The field of agricultural sciences in which the production of newer variety of high yielding, pest and disease resistant, and cost effective agricultural plants are developed by using the biotechnology based concepts of mutagenesis, rDNA technology and gene cloning.

Medical biotechnology: The area of medical sciences which utilizes the diagnostic aids like the AIDS detection kits, glucose measuring kits etc., and attempts for correction of some hereditary disorders by gene incorporation utilizing the basic concepts of biotechnology is termed as medical biotechnology. The production of artificial organs like the liver and kidney are the emerging fields of the subject.

Engineering biotechnology: The utilization of biotech based enzyme sensors for chemical process monitoring, utilization of some genetically modified strains of microbes as an aid in the chemical synthesis, degeneration of the industrial wastes by some cloned bacteria are grouped together and referred as engineering biotechnology.

Biomedical Engineering: Preparation of some artificial organs as an option or replacement alternative for the vital organs lost due to accident or birth disorders utilizing the biotechnological concepts like polymer engineering, enzyme immobilization etc. is known as biomedical engineering.

Textile and Paper Biotechnology: The application of the concepts of biotechnology as the polymer engineering, production of some special microbe strains, as well as process monitoring using biotech based sensors in production of special fibers is termed as textile biotechnology. The same implies for the paper biotechnology. Furthermore, the immobilization of the enzymes being utilized for the production can further support in the cost effective production of better quality textile and paper.

Environmental biotechnology: The destruction of the wastes from industrial, urban or other sources utilizing specially cloned micro-organisms is a major application that is a part of deals with environmental biotechnology. It also uses the techniques for the purification of the waste water as well as the industrial wastes, safe to be discharged into the rivers or sea.

Mining and Metal Biotechnology: This is a field which has been undergoing expansion during this decade. It utilizes the concept that there are some groups of micro-organisms which erode the surface of the metals; *Thiobacillus ferroxidans* oxidizes sulfur and iron present in the soil, *Leptospirillum ferroxidans, T. organoparpus* degrade pyrates (FeS_2) and Chalcopyrite ($CuFeS_2$). This branch deals with the isolation of the micro-organisms which are capable of affecting these types of degradation and utilizes them in the isolation and purification of the metals and minerals.

Leather Biotechnology: Leather industry is based on the tanning of the skin from the animals using various enzyme systems. The development in the field of enzyme immobilization technology has offered the advantage for the automation of the technology and more cost effective treatment of the leather.

Pharmaceutical Biotechnology: It is a major branch of biotechnology undergoing fast development. The concepts based on biotechnology, in the production of the therapeutic proteins and hormones, fermentation products like the antibiotics, specially designed vaccines or drug design using the receptor hypothesis, gene correction, drug delivery to specific tissues (targeted delivery), production control using the biosensors, artificial bioprostheses, standardization of chemotherapeutic agents and the diagnostic aids using the gene cloning technology, recombinant DNA technology, enzyme immobilization, monoclonal antibodies and mutagenesis have been exploited and attempted for possible use. Furthermore, all the fields of medical biotechnology have to be linked with the pharmaceutical biotechnology in order to attain the approvals from FDA.

The last few decades have witnessed some revolutionary advancements in biological sciences which have dramatically affected the future of design and development of pharmaceuticals in an unprecedented manner. The concept of molecular biology and biotechnology has altogether changed the scenario of pharmaceutical developments. Emergence of DNA cloning technology, known commonly as recombinant DNA (rDNA) technology and the methodologies for production of monoclonal antibodies called hybridoma technology, are the counter pieces of revolution, which are the outcome of decades of continual basic research directed towards molecular biology, cell biology and immunology. Similar developments in the field of biological sciences, commonly referred as 'biotechnology', have facilitated the development, designing, discovery, as well as production of drug(s). Not only drugs but also the technology for better therapeutics and diagnostics have been put forth.

Some major advancements in the field of pharmaceuticals in the last few decades have come forth as a result of extensive research and advancement in pharmacology, analytical chemistry, synthetic organic chemistry, biochemistry and drug delivery. The field of biotechnology has thus an attractive opportunity for maximum developments. It is 10 years now after FDA approval was granted for the first biotechnological product, recombinant human insulin; over 100 products derived from biotechnological principles have progressed to the stage of clinical use or human trials. Over the next 10 years, the global sale for biotechnology based products is expected to approximate $30 billion per annum. It is therefore abundantly clear that the practice of pharmacy has been and will continue to be, strongly influenced by the field of biotechnology and the practicing pharmacist should surely understand the concepts now being created. Some milestones in the history of pharmaceutical biotechnology are listed in table 1.1.

The production of enzyme or hormone based pharmaceuticals has been revolutionized by the recombinant DNA technology. Consider the case of insulin; since its discovery in 1921 by Banting and Best, many animals have been sacrificed so as to achieve very small quantities of the protein. However, since 1986 the recombinant production process has overtaken the markets. The human genetic coding for proinsulin is inserted in *Escherichia coli* cells, which were then grown by fermentation to produce proinsulin. The connecting peptide was further cleaved and converted enzymatically from proinsulin to human insulin. Currently the product is being manufactured by Eli-Lilly and company. The recombinant DNA technology offered many added advantages like production of non-immunogenic, more effective, cheaper products, sparing animal life too.

It has been a subject of debate for years as to how to define pharmaceutical biotechnology as well as how to justify the nomenclature. It was evolved out of vigorous discussion, that as pharmaceutical aspects of chemistry and analysis were respectively accepted as pharmaceutical chemistry or pharmaceutical analysis, it appears to be appropriate to accept the name for the field that encompasses pharmaceutical aspects of biotechnology as pharmaceutical biotechnology. Obviously the products which occur naturally and of microbiological or biological origin having applicable potential in pharmaceutical industry in human therapeutics, in disease diagnosis as well as clinical monitoring of patients may largely be covered under the discipline of pharmaceutical biotechnology. Obviously, the major areas which could be considered include antibodies as microbial secondary metabolites, monoclonal antibodies, genetic engineering and related products, enzyme products, microbial steroid conversion, recombinant vaccine, single cell proteins, animal and plant cell cultures for production of pharmaceuticals, immunomodulators, blood products, tissue banks, protein hydrolysates, and glandular products. Furthermore, other products which too belong to biologicals may include sera, diagnostic agents, organic acids, vitamins, nucleotides, oligonucleotides, antisense, plasma expanders, alkaloids, sutures and ligatures and other microbiological products used in diagnostic and biological assays.

Table 1.1 : Milestones in biotechnology

(The unprecedented development and growth of biotechnology has been an outcome of some of the following mentioned successive, discrete milestone discoveries and events in basic biological research)*.

S. No.	Milestone	Scientist and Year
1.	Proposed double helix model for 3 dimensional structure of DNA after X-ray diffraction data	R.E. Franklin and M. H. Wilkins; J.D Watson and F.H. Crick, 1952-1953
2.	Cleavage of DNA by restriction endonucleases	W. Arber, 1962; M. Meselson and R. Yuan, 1968
3.	Determination of genetic code	M. Nirenberg, S. Ochoa and P. Heder, 1966; H.G. Khorana, 1966
4.	Identification of DNA ligase	M. Gellert, 1967
5.	DNA cloning techniques	H.W. Boyer, S. Cohen and P. Berg 1971-1972
6.	Emergence of rDNA technology	Bordon Conference on Nucleic acids, June 1973
7.	Hybridoma creation	C. Milstein and G. Kohler, 1976
8.	Guidelines issued by Recombinant Advisory Committee (RAC)	1976
9.	DNA sequencing technology	F. Sangar, 1977; W. Gilbert, 1977
10.	US approval of first diagnostic kit using monoclonal antibody technology (MAb)	Anti-C3d Bioclone: Orthro diagnostics 1981
11.	US approval for first pharmaceutical product derived from DNA technology [Human Insulin (Humulin)]	Genetech and Eli Lilly and Co. 1982)

**Huber, B.E., FASEB, 3(1), 1989, 5*

A concept central to pharmaceutical development is the postulation of the presence of 'receptor substances' in biological systems to which drugs would bind with specificity, thus eliciting their responses. Receptor concept has been propounded by Ehrlich from his studies of antigen-antibody interaction and binding of dye to cells. Earlier developments in drug discovery were based upon hypothetical receptor mediated drug action since methods for isolation of receptors were not established.

The new technological advancements of recombinant DNA and monoclonal antibody technology address the receptor site of the drug selectively and enable scientists to have real understanding of mode of the drug action mechanism. The ability to obtain detailed structure of receptors and the molecular ligands using biological analysis of the gene sequence, production of receptors in large quantities for structural analysis and development

of specific antibody reagents to analyze their presence in organs and tissues have opened new vistas for newer drug development and for modification of old drug entities.

The recombinant DNA technology may be appreciated as a milestone which has led to a qualitative and quantitative growth in research in the field during this century. Some of the products originating from genetic engineering are clotting factor, colony stimulating factors, dismutases, erythropoietins, MAbs, recombinant soluble CD4, tumor necrosis factor and tissue plasminogen. Using monoclonal antibodies a variety of diagnostic kits have been developed. Some of the classical advents include: ovarian cancer detecting test, and kits for detection of tumor in stomach and intestine as well as kits for pregnancy testing. The diagnostic kits developed are of greater precision, accuracy and reproducibility. Similarly, immunoradiometric assay kits for measurement of interferon or other autocoids are interesting examples of biotechnological development which have significantly contributed towards diagnostic pharmaceuticals. The hybridoma technology which provided pivotal base for monoclonal antibody production is one of the important inventions in biotechnology on which what we call modern pharmaceutical biotechnology mainly depends upon. The most important utilization of the hybridoma based antibodies is their specific utilization in the target oriented therapy so as to attain cell specific delivery of the drugs like anticancer and anti-HIV drugs etc.

Enzyme related products which nearly count two dozen are employed in therapeutics and preventive medicine. The therapeutic values are mainly classified to be as clotting factor, digestive aids, antithrombolytic agents, diffusive enzymes, anti-inflammatory enzymes and some specifically designed or aimed enzymes (e.g. urokinase, chymotrypsin, penicillinase, glucocerbrosidase, streptokinase, etc.). One of the various functions of an enzyme is biochemical conversion which has been greatly exploited for the conversion of racemic DL-amino acids to biologically active α-amino acids tyrosine to L-dopa, etc. Similarly the steroidal conversion where the conversion products are of pharmaceutical importance, have been reported using free and immobilized enzyme systems as well as immobilized microbial cells.

Effect of most of the drugs is through interaction with molecular constituents of cells. Amongst these nucleic acids, mainly DNAs are the receptors for a variety of chemotherapeutic agents used in the treatment of cancer. In the wake of the detailed understanding of gene expression provided by molecular biological tools, newer therapeutic approaches of targeting to nucleic acids are under development. An analysis of cellular carbohydrates, which are often linked to proteins, promises newer opportunities for drug development. This area named as '**glycobiology**' could be identified as one of the recent developments in biotechnology. In a very similar direction, an in depth knowledge of cell biology has revealed the importance of lipids and lipid conjugates in cellular functioning. These molecules play a vital and structural role in anchoring proteins to membranes. Lipids and lipid derivatives are involved as intracellular effectors in the pathways of transduction of extracellular signals.

The most beneficial part of biotechnology is the ability to produce therapeutically active proteins and peptides. Use of therapeutically active proteins and peptides predates the developments in pharmaceutical biotechnology. For instance antihaemophilic factor VIII, immunoglobulin fraction isolated from human sources were well established prior to the advent of recombinant DNA techniques. But due to reasons of safety and low production rates they could not be adopted and exploited as therapeutics. Recombinant materials revolutionized the production of peptides. Now they can be produced in large quantities.

Proteins and peptide based drugs have been extensively utilized in replacement therapies in cases where the patient is unable to produce the required protein in sufficient quantities as in the case of insulin in Type I diabetics. The case of subunit and peptide vaccines represent the class which has been utilized for their improved therapeutic potential due to their ability to produce large quantities of proteins with directed changes in primary sequences. The development of the recombinant based protein products is increasing day by day like growth hormone, interferons, interleukines, cytokines. It could well be concluded that the field of professional pharmacy is being affected significantly by biotechnology.

1.2. PHARMACIST AND BIOTECHNOLOGY: A NEWER RESPONSIBILITY

The introduction of biotechnology based products has introduced newer responsibilities to be realized by the pharmacist. Throughout, the history, pharmacy has successfully adapted to the changes within the pharmaceutical industry and medicine. Now the biotechnology revolution has presented pharmacy with a unique challenge. If they are to meet these new challenges successfully, pharmacists must continue to fulfill their existing responsibilities while developing additional roles.

Evaluating the new products is one way that pharmacy can adapt itself to the changing medical environment. Although new biotechnology products are often assumed to be better than the standard therapeutics, in some cases the existing therapies may be equally efficacious and less expensive for the patient and the health care systems. For example, alteplase is considerably more expensive than other fibrinolytic compounds but may be no more effective. Pharmacists should promote sound scientific judgment in selecting new agents for formulary inclusion.

Recent advances in understanding of the immune system, genetics, recombinant DNA, hybridomas, and monoclonal antibodies have led to a rapid increase in the number of biotechnological products. Substantial investments by government agencies in basic biotechnology research and applied industrial research have resulted in the development of at least 81 biotechnology drugs and vaccines for human use (1990). The new products offer promise for the treatment of a wide variety of disorders in virtually every medical subspecialty, including oncology, hematology, cardiology, immunology, and endocrinology. As the knowledge base for biotechnology continues to expand, future research may shift its focus from treating disease to preventing it through gene therapy and the development of genetically engineered vaccines, and other pharmaceuticals.

The rapid expansion in the field of biotechnology products has presented new opportunities for the pharmacist while creating a new set of responsibilities. These responsibilities provide new opportunities for the pharmacist so as to develop newer skills and expand their role in clinical pharmacy services, clinical research, drug distribution and drug information. However, to retain responsibility for the dispensing of the new biotechnology products pharmacists must keep abreast of innovation in this area, including the development of the new drug-delivery systems and expanding contemporary pharmacy services, to fulfill the unique demands imposed by the new products.

The most developing field of biotechnology in which the pharmacist has to work extensively is the unique drug and drug delivery systems. They are a complex and a newer variety of the pharmaceutical agents with which the pharmacist must become familiar. Further complicating the picture is the fact that many of the new biotechnology products are proteins that are targeted towards the specific uses. Most of them also have very short half life and may require unique delivery systems because simple oral administration is generally not possible.

Strategies for drug delivery currently being explored, include encapsulating the drug in the coating(s) that protects it until absorption can occur, combining the drug with the biodegradable polymer, enclosing the drug in the liposomes or other vesicular carriers or red blood cells before directing the drug to the specific site and then modifying the surface so as to achieve the targetability, designing transdermal and nasal delivery systems, delivering the agents as prodrugs that undergo biotransformation *in vivo*, combining the drug with the monoclonal antibodies that will attach to a specific target providing the proteins and the other therapeutic hormones in a deterred environment so as to protect from the lytic system(s) of the body. Other approaches focus on a variety of controlled drug release systems or implantable drug pumps.

Not only the specialized delivery system but also the development of the artificial organs and the blood purification systems is offering newer responsibility to be shouldered by the pharmacist especially in undertaking the clinical trials. The artificial liver developed by the encapsulation of the hepatocytes and

bypassing the diseased liver by a blood circuit offers a major challenge for the pharmacist. Furthermore, the development of the blood purification systems based on the *ex-vivo* separation of the plasma from the cells and its purification and reconstitution has offered a further responsibility to the pharmacist. Hence it could be stated that although the development in the field of the pharmaceutical biotechnology has led to a number of products into the market it has also led to a major challenge for the pharmacist to tackle. The newer responsibility has made the understanding of the subject more desirable and vital in the modern pharmaceutical scenario.

1.3. BIOTECHNOLOGY AND INDUSTRY

In essence, biotechnology may be defined as the collection of industrial processes that involve the use of biological systems. As compared to pharmaceutical drug development, the history of industrial biotechnology is quite short. In chronological order, after the discovery of genetic engineering and monoclonal antibody related technologies, their commercialization began in 1970's. Small biotech concerns entered the area, whereas large capital concerns were slow to take up biologically oriented drug discovery program.. Genetech was the first biotech based concern to be launched by Eli-Lilly in early 80's. Since then many concerns have been formed. At present, a high proportion of international biotechnological efforts are concentrated mainly in the US. In 1992 'Genetic Engineering-The News Guide to Biotechnology Companies', 737 companies from 25 countries have been listed, out of them, 547 are from the US. A more recent report puts the number of biotechnology based companies in the US to be 742 with a majority of these focusing on the development of therapeutic agents.

The impact of biotechnology on the pharmaceutical industry is changing quickly. 'Traditional biotechnology', in the form of antibiotic production is still much more valuable in commercial terms than the 'modern biotechnology' involving genetic engineering. The antibiotic market is worth $10 billion annually or about 5% of the total pharmaceutical market. By contrast the total sales from the much heralded revolution, through therapeutic proteins still lags well behind any one small molecule blockbuster. However, there are several areas where molecular biology and genetic engineering are influencing drug discovery and drug development. In particular, the techniques have provided humanized antibodies, new insight into the disease mechanism and novel functional assays including cloned and expressed human receptors and transgenic mice.

Initially, small biotech concerns of early 80's focused their major efforts on improved production of therapeutically active proteins such as insulin, factor VIII and human growth hormone. However, after the discovery of Interferon, an antiviral protein for its anticancer activity, major interest of pharmaceutical biotechnology has shifted. Further, the major attention seems to shift towards the other less established natural proteins which were available in small quantities such as clot-dissolving protein, cell growth factors, tissue plasminogen activator, etc. With the involvement of multinational pharmaceutical concerns in the development of therapeutic proteins more funds could be localized and with their previous experience in clinical trial based studies, some major breakthroughs could be anticipated. Since this brought into existence a newer class of drugs, the Food and Drug Administration (FDA) and other approving authorities had to enforce and enact some newer laws and regulations in order to take care of the safety of such products. As a source of guidance to biotech industry, several 'points to consider' include documents dealing with different aspects of biological drug approval process have been published by FDA in the US.

Within such a short period of time, the pharmaceutical drug discovery, drug production and drug delivery aspects have been revolutionized so much that every major pharmaceutical concern has some in-house research efforts in biotechnology and many have gained access to select technologies through alliances with or ownership of smaller biotechnology companies. It could now be said that 'biotechnology is an integral part of pharmaceutical R&D'. The early years of biotechnology offered some dazzling challenges and high prospects for financial investments. Although initial expectations have been somewhat unfulfilled, about 100 'biotech' drugs are at various stages of clinical development and over a dozen have won FDA approval. Broadly they could be grouped as blood products, immunotherapeutics, infectious disease products. Table 1.2 mentions some of the biotechnologically derived products which have obtained FDA approval. There are still hundreds which

are in some phase of clinical trials and some others have been forwarded for approval. Some of these products are listed in table 1.3 separately.

After considering all the factors it would be fair to state that biotechnology in the last few decades has become a part of pharmaceutical development. The recent decade in particular has seen some unprecedented developments in this field. Further, the developments will have an impact on the practice of medicine and on the pharmaceutical industry. Although this impact at present is unpredictable, exciting pathway are bound to open up carrying us into the twenty-first century.

Table 1.2 : Biotechnological drugs and vaccines tested and approved until 1992

S. No.	Generic Name	Product Name	Company	Approval Date
1.	Human insulin	Humulin	Eli Lilly	Oct., 1982
2.	Sometrem	Protropin	Genetech	Oct., 1985
3.	DigoxinImmune Fab	Digibind	Burroughs Wellcome	April, 1986
4.	Muromonab CD3	Orthoclone OKT3	Ortho Biotech	June 1986
5.	Interferon-α-2b	Intron A	Schering-Plough	June 1986
6.	Interferon-α-2a	Roferon-A	Hoffmann-La-Roche	June 1986
7.	Hepatitis-B-vaccine	Recombivax HB	Merk	July 1986
8.	Somatotropin	Humatrope	Eli Lilly	March 1987
9.	Alteplase	Activase	Genetech	Nov., 1987
10.	Heamophilus-B-conjugate vaccine	Hib Titer	Praxis Biologics	Dec., 1988
11.	Epoietin-α	Epogen	Amgen	June 1989
12.	Hepatitis-B-vaccine	Engerix-B	SmithKline Beecham	Sept., 1989
13.	Interferon-α-n3	Alferon N	Interferon Sciences	Oct., 1989
14.	Interferon-γ-Ib	Actimmune	Genetech	Dec., 1990
15.	Filgrastim	Neupogen	Amgen	Feb., 1991
16.	Epoitin-α	Procrit	Ortho Biotech	Feb., 1991
17.	Sargramostim	Prokin	Hoechst-Roussel	March 1991
18.	Sargramostim	Leukin	Immunex	March 1991
19.	Aldesleukin	Proleukin	Cetus	June, 1992

1.4. GMP COMPLIANCE AND BIO-PHARMACEUTICAL FACILITIES

Recent years have witnessed an explosive growth in the biotechnology industry in the area of development and manufacture of a variety of new products. Most of the interest has been focused on the development of biopharmaceutical products such as vaccines, therapeutic proteins and monoclonal antibodies.

The development activity has reached a point where companies are commercializing their products. Being the most developed country, in USA alone companies such as Genetech, Amgen, Centocor and others have brought products into the market. Some other companies have contracted with them around the globe for designing and construction of manufacturing facilities for these products in compliance with the FDA and cGMP. Most of the biopharmaceuticals being developed are derived from the application of recombinant DNA technology. For regulatory purpose, most of these products are classified as **biologicals**. It is important to recognize that United States FDA has two main regulatory groups with the responsibilities for different therapeutic products.

In most of the countries of the world and especially in Indian based concerns the regulatory considerations applicable are very similar to those in the FDA of United States. The Center for Drug Evaluation and Research (CDER) is concerned with the traditional products that are produced by fermentation or organic synthesis and which are readily characterized with well defined analytical methods. These include antibiotics, analgesics, anti-inflammatory agents, etc. Most of the recombinant therapeutic products with the exception of insulin are regulated by the Center for Biologics Evaluation and Research (CBER). Traditionally, CBER was responsible

for the regulation of vaccines, blood products and other natural products. CBER has framed strict rules of compliance in their regulations for biotechnological products because of their distinctiveness from chemical drugs.

Biologicals differ from the pure chemical drugs in the following respects:

1. They are derived from living organisms
2. These products are typically complex biochemical mixtures
3. Biologicals are usually difficult to assay and quantify

Table 1.3 : Biotechnological products which have been in process of approval until 1992

S.No	Product Name	Company	US Development Status
1.	Superoxide dismutase	Bio-Technology General, Bristol Mayers	Phase II
2.	PEG-SOD (Superoxide dsmutase)	Sterling Drugs, Enzon	Phase II/III
3.	Morgens srile pwder (Epoietin-β)	Genitics Institute, Chugai-Upjohn	Application submitted
4.	Eprex	Ortho-Pharmaceuticals	In Human clinical trials
5.	Prourokinase	Collaberative research, Sandoz	Phase II/III
6.	Tissue pasminogen activator	Genetics Institute, Wellcome Biotechnology	Phase II/III Application pending
7.	Nupogen (Granulocyte/ colony stimulating factor)	Amgen	Phase III
8.	Granulocyte macrophage/ colony stimulating factor	Amgen	Phase II/III
9.	KoGENate (Factor VIII)	Cutter Biologicals	Application submitted
10.	Recombinant factor VIII	Bexter Healthcare, Genetics Institute	Phase I
11.	Mono-IX (Factor IX)	Rhone Poulene Rorer	Application submitted
12.	Insulin like growth factor I	Chiron, Ciba-Geigy	Phase I
13.	Norditropin (Somatotropin)	Novo Nordisk	Application submitted
14.	Saizen (Somatotropin)	Senoro Laboritories	Application submitted
15.	Bio tropin	Genetech	Application submitted
16.	VaxSyn® HIV-1	MicroGeneSys	In clinical trials
17.	HIVAC-le vaccine	Bristol Mayer/Oncogen	Phase I
18.	Alferon Gel (interferon-α-2b)	Busch Biotech	Application submitted
19.	Betaseron (interferon-β)	Berlex Laboratories	Phase III
20.	Centoxin (HA-1A Mab)	Centocor	Application submitted
21.	E5 (Mab)	Pfizer, Xoma	Application submitted
22.	XomaZymase-CD5 Plus (Mab)	Xoma	Application submitted
23.	Orthozyme CD5 (muromonab CD5-RTA)	Ortho Biotech	Application submitted
24.	DNase (rh DNase)	Genetech	Phase III

4. In many instances the correlation of the assays with biological and clinical activity is difficult
5. These products are usually susceptible to damage from heat and/or shear stress.
6. The loss of configuration is difficult to control
7. These products are susceptible to contamination from many sources.

Due to these differences and CBER's past experience with vaccines and blood products, their regulatory approach differs form CDER in two major ways; first, product approval strategies and second, in the application of GMP's to all stages of the manufacturing even to the earliest stages of cell culture maintenance and inoculum scale-up. Because of the GMP and licensing requirements, the design of the manufacturing unit and facilities is very important. Plant design and layout is crucial for effective control of people and material flow facilities. The design and the specifications of the materials for plant process and utility systems are critical for

reproducible processing, prevention of the product contamination and effective clean-in-place capabilities. Finally, the entire facilities must be validated.

According to the GMP considerations the major requirements are:

1. the use of recombinant organisms requires the identification of the contaminant level tolerable and identification of those processing areas requiring corrective measures;
2. the layout of the work areas which address the need to protect the product from contamination during processing;
3. the particular requirement of the bulk production including culture maintenance, media and the buffer preparation, inoculum scale up, fermentation, product recovery and purification and the finishing aspects which include operation such as formulation, filling and packaging.

The US regulatory requirements for architectural consideration for the biopharmaceutical building are presented in 21CFR, parts 210, 211 and 212. The specific intent of these regulations is to provide broad guidelines without detailed specifications for the designing facilities. In this way the technological improvement can be incorporated without the need to rewrite the regulations. In the case of biopharmaceuticals the FDA is particularly interested in the details of the facility layout. The flow of people and material through the facility is as important as the traditional mass and energy balance the process. Integration of the building design with the process system is highly imperative.

SUGGESTED READINGS

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