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Review Article

A SYSTEMIC REVIEW ON BIOTECHNOLOGICAL PRODUCTS AVAILABLE IN CURRENT PHARMACEUTICAL MARKET

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ABSTRACT

Over the past few decades' biotechnology – sometimes described as the oldest profession in the world – has evolved into a modern technology without which medical progress would be scarcely imaginable. Modern biotechnology plays a crucial role both in the elucidation of the molecular causes of disease and in the development of new diagnostic methods and better targeted drugs.

These developments have led to the birth of a new economic sector, the biotech industry, associated mostly with small start-up companies. For their part, the more established healthcare companies have also been employing these modern techniques, known collectively as biotechnology, successfully for many years. By studying the molecular foundations of diseases they have developed more specific ways of combating diseases than ever before. This new knowledge permits novel approaches to treatment, with new classes of drug – biopharmaceuticals – attacking previously unknown targets.

This short report has attempted to analyze some of the important areas of biotechnology. The focus was on the organism aspects of biotechnology and not on the more complex areas such as dewatering, drying, and extraction/purification. We shouldn't expect too much too soon from biotechnology. There are some very promising results that have been obtained from ongoing experiments, but there is still a long way to go. Things like insulin and monoclonal antibodies should become available quite quickly so a simple classification of all the biotechnological products is given here for an easy market use.

Keywords: biotechnology, biopharmaceuticals, monoclonal antibodies, pharmaceutical market.

INTRODUCTION

Biotechnology is the application of biological organisms, systems or processes to manufacturing industries. Biotechnology firms will rely mainly on inexpensive substrates for biosynthesis, processes that will function at low temperatures, and will consume little energy. (1) There will be numerous industrial activities that will be affected by the biotechnological advances which include human and animal food production, provision of chemical feedstocks to replace petrochemical sources, alternative energy sources, waste recycling, pollution control, agriculture, and new products to aid in the advancement of medicine, veterinary sciences, and pharmaceutics. Biotechnology is a relatively new area and will require skilful control of its development. (2) There are many areas of application of biotechnology. (3)

BIOTECHNOLOGY AND MEDICINE

Antibiotics are antimicrobial compounds produced by living organisms and are used therapeutically and sometimes prophylactically in the control of infectious disease. Over 4000 antibiotics have been isolated but only about 50 have achieved wide usage. (4) The other antibiotic compounds failed to achieve commercial importance because of their toxicity to man or animals, lack of producing the desired effect, or high production costs.

Penicillin was the first antibiotic introduced in the market for human use from a fungus. (5)

Antibiotics may function over a wide range of microorganisms and are termed 'broad spectrum', for example chloramphenicol and the tetracyclines which can control such unrelated organisms as the rickettsiae, chalamydiae, and mycoplasma. (6) In contrast, streptomycin and penicillin are examples of narrow spectrum antibodies being effective against only a few bacterial species. Most antibiotics have been derived from the actinomycetes and the mould fungi.

Thus, in medicine, biotechnology will have an increasing importance in the production of new and improved products that will contribute to the well-being of mankind. Such benefits must not be limited only to the developed nations and it must be hoped that the new medically related biotechnologies can be transferred in some form to the more needy developing countries where disease are still such crippling forces.

HOW DO BIOTECHNOLOGY MEDICINES DIFFER FROM OTHER MEDICINES?

A medicine is a therapeutic substance used for treating, preventing, or curing disease. The most familiar type of medicine is a chemical compound contained in a pill, tablet, or capsule. Examples are aspirin and other pain relievers, antibiotics, antidepressants, and blood pressure drugs. This type of medicine is also known as a small molecule because the active ingredient has a chemical structure and a size that are small compared with large, complex molecules like proteins. (7) Most medicines of this type can be taken by mouth in solid or liquid form. Biotechnology medicines, often referred to as biotech medicines, are large molecules that are similar or identical to the proteins and other complex substances that the body relies on to stay healthy. They are too large and too intricate to make using chemistry alone. Instead, they are made using living factories—microbes or cell lines—that are genetically modified to produce the desired molecule. A biotech medicine must be injected or infused into the body in order to protect its complex structure from being broken down by digestion if taken by mouth. (8)

In general, any medicine made with or derived from living organisms is considered a biotech therapy, or biologic. (9) A few of these therapies, such as insulin and certain vaccines, have been in use for many decades. Most biologics were developed after the advent of genetic engineering, which gave rise to the modern biotechnology industry in the 1970s. Amgen was one of the first companies to realize the new field's promise and to deliver biologics to patients. Like pharmaceuticals, biologics cannot be prescribed to patients until their use has been approved by regulators.

HOW ARE BIOTECHNOLOGY MEDICINES MADE?

The manufacture of biologics is a highly demanding process. Protein-based therapies have structures that are far larger, more complex, and more variable than the structure of drugs based on chemical compounds. Plus, protein-based drugs are made using intricate living systems that require very precise conditions in order to make consistent products. The manufacturing process consists of the following four main steps: (10)

1. Producing the master cell line containing the gene that makes the desired protein
2. Growing large numbers of cells that produce the protein
3. Isolating and purifying the protein
4. Preparing the biologic for use by patients

Some biologics can be made using common bacteria, such as E coli. Others require cell lines taken from mammals, such as hamsters. This is because many proteins have structural features that only mammalian cells can create. For example, certain proteins have sugar molecules attached to them, and they don't function properly if those sugar molecules are not present in the correct pattern. (2) (5)

Table: 1 Biotechnology techniques and processes used to produce biotechnological medicines

Polymerase chain reaction	Bioinformatics
Recombinant DNA proteins	Molecular engineering
Monoclonal antibodies	(AA/CHO/PEG/fusion) Peptides
Structure activity relationship	Receptors
Genomics	Animal-based products
Gene therapy	Marine-based products
Ribozymes	Tissue engineering
Nucleotide blockade	Cell therapy
Pharmacogenomics	Virology
Transgenic animals	Formulations
Combinatorial chemistry	Liposomes/Polymers
High throughput screening	Biogenerics
Protein kinases	Proteomics

HUMAN APPLICATIONS

☐ Biotechnology derived drugs are being applied in cancer therapy, HIV, AIDS and AIDS-related and autoimmune diseases

☐ In diagnostic investigations

☐ As blood substitutes, clotting factors, etc.

☐ Human insulin (approved in 1982) and human growth factor were the first set of biotechnology products to be applied for human therapy. (4) (6)

☐ Systemic growth hormone - Somatropin recombinant Humatrope®

☐ Colony stimulating factors -

☐ Erythropoietin

☐ Interferon

☐ Vaccines – Genetically engineered vaccines use a synthetic copy of the protein coat of a virus to "fool" the body immune system into mounting a protective response. (4) (6)

Table 2: Approved biological: Interferon's [11], [12]

GENERIC NAME	BRAND NAME (COMPANY)	THERAPEUTIC AREA
Interferon alpha-n1	Welferon (Glaxo SK)	Chronic hepatitis
Interferon alpha-2a	Roferon-A (Roche)	Hairy cell leukemia AIDS-related Kaposi's sarcoma Chronic myelogenous leukemia
Interferon alpha-2b	Intron (Schering-Plough)	Hairy cell leukemia AIDS-related Kaposi's sarcoma Chronic hepatitis b and c Condylomata accuminata Malignant melanoma Follicular lymphoma Non-hodgkin's lymphoma
Interferon alpha-n3	Alferon N (Interferon Sciences)	Condylomata accuminata (genital warts)
Interferon gamma-1b	Actimmune (Genentech)	Chronic granulomatous disease osteoporosis
Interferon beta-1b	Betaseron (Berlex/Chiron/Novartis)	Acute relapsing-remitting multiple sclerosis
Interferon beta-1a	Avonex (Biogenldec) Rebif (Serono/Pfizer)	Acute relapsing-remitting multiple sclerosis
Peg-Interferon-2a	Pegasys (Roche)	Hepatitis C
Peg-Interferon-2b	PEG-Intron A (Schering-Plough)	Hepatitis C
Interferon-2b + Ribavirin	Rebetron (Schering-Plough)	Hepatitis C
Interferon alpha con-1	Infergen (InterMune)	Hepatitis C (Naive and Relapse)

SOME OF THE PRODUCTS OF BIOTECHNOLOGY

☐ Anticoagulant drug –Lepirudin Refludan®

☐ Antisense drugs – Fomivirsen sodium injection is approved for local treatment of cytomegalovirus (CVM) retinitis in patients with AIDS

☐ Efavirenz (Sustiva®) – A non-nucleoside reverse transcriptase inhibitor and the first anti-HIV drug to be approved by FDA for once daily dosing in combination with other anti-HIV drugs.

☐ Clotting factors - Kogenate®, Recombinate®– Recombinant anti-hemophiliac factor indicated for the treatment of classical hemophilia A in which there is a demonstrated deficiency of clotting factor (Factor VIII)

☐ Growth factor – Becaplemin (regranex®)

Biotechnical methods are now used to produce many proteins for pharmaceutical and other specialized purposes. A harmless strain of Escherichia coli bacteria, given a copy of the gene for human insulin, can make insulin. As these genetically modified (GM) bacterial cells age, they produce human insulin, which can be purified and used to treat diabetes in humans.

Microorganisms can also be modified to produce digestive enzymes. In the future, these microorganisms could be colonized in the intestinal tract of persons with digestive enzyme insufficiencies (13). Products of modern biotechnology include artificial blood vessels from collagen tubes coated with a layer of the anticoagulant heparin. (14) (11)

Table 3: Approved biological: Enzymes [11] [12]

GENERIC NAME	BRAND NAME	THERAPEUTIC AREA
Alteplase (r-TPA)	Activase (Genentech)	Acute myocardial infarction Pulmonary embolism Stroke CVT clot removal
Reteplase	Retevase (centocor/J&J)	Acute myocardial infarction
Tenectaplase	TNKase (Genentech)	Acute myocardial infarction
Tirobifan HCl	Aggrastst (Merck)	Acute coronary syndrome
Eptifibatide	Intergrelin (Millenium/Schering)	Acute coronary syndrome Angioplasties Stenting
Bivalirudin	Angiomax (Medicine Co.)	Coronary angioplasty Unstable angina
Lepirudin	Refludan (Sanofi-Aventis)	Coronary angioplasty Unstable angina
Dornase alpha	Pulmozyme (Genentech)	Respiratory complications of cystic fibrosis
Imiglucerase	Cerezyme (Genzyme)	Type I gaucher's disease
Algasidase	Fabrazyme (Genzyme)	Fabry's disease
Laronidase	Aldurazyme (Genzyme)	Mucopolsaccharidosis I (hurler syndrome)
Galsulfase	Naglazyme (Biomarin)	Mucopolsaccharidosis IV
Peg-ademase	Adagen (Enzon)	Severe combined immune deficiency
Rasburicase	Elitek (Sanofi-Aventis)	Hyperuricemia related to chemotherapy
PEG-L-asparginase	Oncospar (Enzon/Sanofi/Aventis)	Acute lymphoblastic leukemia

Table 4: Approved biological : Vaccines and liposomes [11] [12]

GENERIC NAME	BRAND NAME	THERAPEUTIC AREA
Hepatitis B vaccine	Engerix-B (GlaxoSK) Recombivax HB (Merck)	Hepatitis B prophylaxis
Hepatitis A & B vaccine	Twinrix (GlaxoSK)	Hepatitis A and B prevention
Hepatitis B vaccine	Pediarix (GlaxoSK)	Hepatitis B immunization in children
Haemophilus b and Hepatitis B vaccine	Comvax (Merck)	Prevention of H.influenza b and Hepatitis B
Lyme disease vaccine	LtmErix (GlaxoSK)	Prevention of Lyme disease
Doxorubicin-liposomal	DOXIL (Alza/J&J)	Kaposi's sarcoma
Amphotericin-liposomal	Abelcet (Elan) Amphotec (InterMune) Ambisome (Gilead)	Systemic fungal infection Aspergillosis infection Cryptoccocal meningitis in HIV patient; visceral leishmaniasis
Daunorubicin-liposomal	DaunoXome (Gilead/Astellas)	Kaposi's sarcoma

Table 5: Approved biological: Tissues and cell engineering [11] [12]

GENERIC NAME	BRAND NAME	THERAPEUTIC AREA
Hyaluronidase acid membrane	Seprafilm (Genzyme)	Prevention of adhesion after surgery
Hyaluronidase acid gel	Adcon-L (Giatech)	Prevention of adhesion after lumbar surgery
Sodium Hyaluronidase	Nuflexxa (Savient)	Pain with osteoporosis of knee
Hyaluronidase acid formulations	Orthovisc (Anika/Ortho-Biotech) Captique (Genzyme/Inamed) Synvisc (Genzyme)	Pain with osteoporosis of knee Facial wrinkles and folds Facial wrinkles correction Pain with osteoporosis of knee
Hyaluronidase-rH	Hylenex (Halozyme Therap.)	Hyperdermoclysis ; aid in drug absorption
Hyaluronidase, ovine	Vitrase (Ista)	Aid in drug absorption
Collagen matrix	FortaFlex (Oranogenesis)	Rotator Cuff repair
Bone graft/Cage (rBMP with metal cage)	Infuse bone graft/LT-Cage (Medtronic/Wyeth)	Low back pain from spinal disc degen; tibia shaft rupture
Osteogenic protein I (BMP-7 in putty)	OP-I protein (Stryker Biotech)	Bone reunion
Cartilage culturing service	Carticel (Genzyme)	Cartilage damage in knees
Skin graft product	Apligraf (Oranogenesis/ Novartis) Trancyte (Advanced Tissue) Integra (Interga/Ethicon) Dermagraft (Smith & Nephew) Orcel (Ortec International)	Wound healing of venous leg ulcers; diabetic foot ulcers Skin repair fro burns Burns; scar repair Diabetic foot ulcers Burns; epidermolysis bullosa
Poly-L-lactic acid	Sculptra (Dermik)	Facial lipodystrophy in HIV/AIDS

Table 6: Approved biologicals -blood derivatives and natural extracts [11] [12]

GENERIC NAME	BRAND NAME	THERAPEUTIC AREA
Albumin-h	Albutein (Alpha therapeutics)	Hypovolemis shock, Haemodialysis, Cardiopulmonary bypass surgery
Calcitonin salmon	Fortical (unigene labs)	Postmenopausal osteoporosis
CMV immune globulin	CytoGam (Med Immune)	CMV disease prevention
Human immune globulin	Gammagard (Baxter)	Primary immune deficiency
Human immune globulin	Venoglobulin-S (alpha therapeutics)	Primary immune deficiency Idiopathic thrombocytopenic purpurea Kawasaki disease
Hepatitis- B immune globulin h	Nabi-HB (Nabi)	HbsAg exposure in hepatitis B patient
Vaccinia globulin IV	Vaccinia Glogulin (Cangene)	Vaccinia infections
Immune globulin vaccinia	DynPort vaccine	Vaccinia infections
Immunoglobulin IV	Octagam (Octapharma)	Primary immune deficiency
Rho immune globulin	Rhophylac (ZLB Biopharma)	Haemolytic disease in new borns
Rho D immune globulin	WinRho SDF (nabi)	Immune thrombocytopenic purpurea
Antithymocyte globulin	Thymoglobulin (sangstat/genzyme)	Kidney transplant rejection
Collagen dermal filler	CosmoDerm (Adv. Tissue Sci./Inamed)	Wrinkles
Botulinium toxin-B	Myobloc (Elan)	Cervical dystonia
Botulinium toxin-A	Botox cosmetic (Allergen)	Strabismus, Blepharospasm, Glabellar lines, Cervical dystonia, Axillary hyperidrosis
Bacillus calmette-Guerin	Pacis (Shire)	Bladder cancer immunotherapy
Anti haemophilic factor-h	Alphanate (Alpha therapeutics)	Haemophilia A
Anticoagulation factor-h	AlphaNine (Alpha therapeutics)	Haemophilia B

Experts in United States anticipate the world's population in 2050 to be approximately 8.7 billion persons. (15)The world's population is growing, so crop requirement will also increase. By increasing crop yields, through the use of biotechnology the constant need to clear more land for growing food is reduced.
(16)

NATIONAL AND INTERNATIONAL BIOTECHNOLOGY POLICY

National governments and international policy making bodies rely on food scientists and others to develop innovations that will create marketable food products and increase food supplies. Governments also rely on scientific research because they are responsible for setting health and safety standards regarding new developments. International organizations can suggest policy approaches and help develop international treaties that are ratified by national governments. (17) Economic success in the competitive international market demands that food production become more efficient and profitable. National governments and international organizations support food biotechnology as a means to avoid global food shortages. Many policy making bodies are also trying to balance support of the food biotechnology industry with public calls for their regulation. Such regulations are necessary to protect public health and safety, to promote international trade, conserve natural resources, and account for ethical issues. (18) (15)

Federal agencies involved in biotechnology regulation include the U.S. Department of Agriculture (USDA) which evaluates agricultural production processes for all foods; the Food and Drug Administration (FDA), which evaluates whole non-animal foods (seafood), food ingredients, and food additives; and the Environmental Protection Agency (EPA), which evaluates plants with insecticidal properties.

CONCLUSION

The applications of biotechnology are so broad, and the advantages so compelling, that virtually every industry is using this technology. Developments are underway in areas as diverse as pharmaceuticals, diagnostics, textiles, aquaculture, forestry, chemicals, household products, environmental cleanup, food processing and forensics to name a few. Biotechnology is enabling these industries to make new or better products, often with greater speed, efficiency and flexibility. Biotechnology holds significant promise to the future but certain amount of risk is associated with any area. Biotechnology must continue to be carefully regulated so that the maximum benefits are received with the least risk. (17) (18)

Biotechnology is at a crossroads in terms of public acceptance. Many Americans have not yet formed a solid opinion on this complex issue. International developments over the next few years will certainly have a major influence on the long-term viability of biotechnology. The future of the world food supply depends upon how well scientists, government, and the food industry are able to communicate with consumers about the benefits and safety of the technology. Several major initiatives are under way to strengthen the regulatory process and to communicate more effectively with consumers. Both the USDA and FDA have opened their regulatory systems to outside review and public comment. The biotechnology industry, university scientists and others are also conducting educational programs (19). These should further strengthen consumer confidence. This partnership among the public and private sectors will support these emerging technologies that will prove vital to the U.S. economy and the developing world in the new millennium. Even Europe will soon find the real benefits of biotechnology compelling.

Biotech drugs have been under development for 25 years but this is still a new and evolving field. The first generation of drugs is being replaced by second and third generation drugs. The future of biotech drugs includes easier and more comfortable routes of administration for patients and Care-givers, new and improved targets, and more sophisticated engineering.

Biotechnology brings production and quality revolution together with wholesomeness and nutritive value of the food products. Biotechnology plays a vital role to improve the quality of livestock products along with ensuring their safety from consumer point of view. New horizons may be explored using biotechnology for preparing nutritive food products with longer shelf life, superior quality as well as more acceptability in consumer market. (20)

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