CONTEMPORARY NATIONAL AND GLOBAL HEALTH ISSUES

Scope/Learning Objectives

This learning material is expected to discuss basic life support skills during emergencies as well as elaborate on the application of biotechnology in pharmacy practice. At the end of the session, participants should be able to:

- Discuss modalities in drug donation, supply and management during emergencies and outbreak of diseases;
- Understand the concept of biotechnology as it relates to development of diagnostic and therapeutic tools and handling of biopharmaceuticals;
- Identify disease control programmes such as (National Malaria Control Programme, National Tuberculosis and Leprosy Control Programme, National Programme on Immunization) and increase the participation of Pharmacists in such programmes.

RAPID RESPONSE AND EMERGENCY PREPAREDNESS (INCLUDING MASS CASUALTY INCIDENTS)

a. WHAT IS AN EMERGENCY?

The term “emergency” is applied to various situations resulting from natural, political and economic disasters. In an emergency, there will usually be unmet health care needs for displaced persons (without medical facilities), or a population with disrupted medical facilities in the immediate aftermath of a disaster. It is important to quantify local needs within the emergency as soon as possible, this will reduce morbidity, mortality and reduce human suffering.

b. WHY PREPARE FOR AN EMERGENCY/ MASS CASUALTY INCIDENT?

i. To reduce human suffering, morbidity and mortality

ii. To contain an infectious disease or minimize injury

iii. To promote quick return to normalcy

c. PROTECTIVE ACTIONS FOR LIFE SAFETY

i. Evacuation: An action to remove from the vicinity of danger

ii. Sheltering: An action to place in a safe house away from site of danger

iii. Shelter-in-place: An action to remain where you currently are

iv. Lockdown: An action to contain spread of risk or minimize spread.

WHO GUIDELINES ON DRUG DONATIONS IN EMERGENCIES

There are many reasons that require medicine donations especially to fulfil events resulting in need for emergency aid, long term aid or assistance to national health systems or to individual health facilities. Donations may come from pharmaceutical companies (directly or through private voluntary organizations), they may come in the form of aid from governments, or they may be donations aimed directly at single healthcare facilities. The intended beneficiaries of donations of medicines range from individual facilities to entire health systems. Although there are legitimate

differences between these scenarios, many basic rules for appropriate donation practice apply to them all

Medicine Selection

a) All medicine donations should be based on an expressed need should be relevant to the disease pattern in the recipient country, and quantities should be agreed between donor and recipient. This may be exempted in acute emergencies on the

condition that the medicine is on the WHO Essential medicines list.

b) All donated medicines or their generic equivalents should be approved for use in the recipient country and should appear on the national list of essential medicines or equivalent or in the national standard treatment guidelines, if the National Essential Medicines List is not updated. Or, if a national list is not available, it should appear on the WHO model lists of essential medicines, unless specifically requested otherwise and provided with a justification by the recipient.

c) The presentation, strength, and formulation of donated medicines should, as far as possible, be similar to those of medicines commonly used in the recipient country.

d) All donated medicines should be obtained from a quality-ensured source and should comply with quality standards in both donor and recipient countries. The WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce4 should be used.

e) No medicines should be donated that have been issued to patients and then returned to a pharmacy or elsewhere, or that have been given to health professionals as free samples.

f) After arrival in the recipient country all donated medicines should have a remaining shelf-life of at least one year. Large quantities of donated medicines become a logistical challenge, even with a long shelf-life. Therefore, based on the national

consumption and available quantities in stock or in the supply chain pipeline, all donated quantities should match the needs to be consumed before they are expired.

Presentation, Packaging and Labelling

a) All medicines should be labelled in a language that is easily understood by health professionals in the recipient country. The label on each container should contain at least the International Nonproprietary Name (INN) or generic name, batch number, dosage form, strength, name of manufacturer, country of manufacture, quantity in the container, storage conditions and expiry date.

b) Donated medicines should be presented in pack sizes that are suitable for the recipient and appropriate to the setting in which they will be distributed or dispensed.

c) All medicine donations should be packed in accordance with international shipping requirements and should be accompanied by a detailed packing list that specifies the contents. The weight per carton should preferably not exceed 30 kilograms. Shipments of medicines should not be mixed with other supplies, unless they are shipped as kits with predetermined contents.

Information and management

a) Medicine donations should be jointly planned, and collaboration between donors and recipients should begin early. Medicines should not be sent without prior consent of the recipient.

b) In the recipient country the declared value of a medicine donation should be based on the wholesale price of its generic equivalent in the recipient country, or, if such information is not available, on the wholesale world-market price for its generic equivalent.

c) Costs of international and local transport, warehousing, port clearance and (customs) storage, handling and disposal or reverse logistics of expired donated products should be paid for by the donor agency, unless specifically agreed otherwise with the recipient in advance.

1. KEY CORE PRINCIPLES FOR MEDICAL DONATIONS

i. donations should benefit the recipient and meet the need of the end user and patient

ii. recipients should be engaged in all stages of t he donation process in order to enable effective coordination and collaboration between the donor and the recipient

iii. donations should be given withbdue respect for the wishes and authority of the recipient, and in conformity with the government policies, regulatory requirements and administrative arrangements of the recipient country

2. QUICK CHECKLIST FOR DONORS

i. The needs of the recipient guide the donation.

ii. Laws, regulations and administrative procedures are respected

iii. National guidelines on drug donation practices are followed

iv. A plan has been agreed with the recipient country

v. Management of disposal of expired or unused products should be agreed in advance

3. QUICK CHECKLIST FOR RECIPIENTS

i. a national donation policy is formulated

ii. needs are specified

iii. responsibility is assigned for allowing entry of useful donations or rejection of unsuitable donations

iv. a registry for recording data on donations is established

v. mechanism for adequate handling of donations are in place

BIOTECHNOLOGY

Biotechnology has continued to advance the state of the art in pharmaceutical research and discovery, especially in the generation and screening of molecular diversity.

Most pharmaceutical products are chemically synthesized but In addition to chemical-based drugs, a range of pharmaceutical substances (e.g. hormones and blood products) are produced by or extracted from biological sources. Biopharmaceuticals, products of biotechnology, come through the use of biological systems (e.g. cells or tissues) or biological molecules (e.g. enzymes or antibodies) for or in the manufacture of commercial products.

Biomedical research continues to broaden our understanding of the molecular mechanisms underlining both health and disease. Since the 1950s, biomedical research has pinpointed a host of proteins produced naturally in the body that have therapeutic applications. Examples include the interferons and interleukins (which regulate the immune response), growth factors, such as erythropoietin (EPO; which stimulates red blood cell production), and neurotrophic factors (which regulate the development and maintenance of neural tissue). Due to the tiny quantities in which these proteins are present in the body, it was not practical to utilize them clinically. The advent of recombinant DNA technology (genetic engineering) and monoclonal antibody technology (hybridoma technology) helped to overcome these difficulties, marking the beginning of a new era of the pharmaceutical sciences. Recombinant DNA technology has had a fourfold positive impact upon the production of pharmaceutically important proteins:

1. It overcomes the problem of source availability. Many proteins of therapeutic potential are produced naturally in the body in

minute quantities. Examples include interferons, interleukins and colony-stimulating factors (CSFs).

2. It overcomes problems of product safety. Direct extraction of product from some native biological sources has, in the past, led to the unwitting transmission of disease. Examples include the transmission of blood-borne pathogens such as hepatitis B and C and human immunodeficiency virus (HIV) via infected blood products.

3. It provides an alternative to direct extraction from inappropriate/dangerous source material. A number of therapeutic proteins have traditionally been extracted from human urine. Follicle stimulating hormone (FSH), the fertility hormone, for example, is obtained from the urine of postmenopausal women, and a related hormone, human chorionic gonadotrophin (hCG), is extracted from the urine of pregnant women.

4. It facilitates the generation of engineered therapeutic proteins displaying some clinical advantage over the native protein product. Techniques such as site-directed mutagenesis facilitate the logical introduction of predefined changes in a protein's amino acid sequence.

Approximately one in every four new drugs now coming on the market is a biopharmaceutical. By mid 2006, some 160 biopharmaceutical products had gained marketing approval in the USA and/or EU. The products include a range of hormones, blood factors and thrombolytic agents, as well as

vaccines and monoclonal antibodies. Many additional nucleic-acid-based products for use in gene therapy or antisense technology are in clinical trials, although the range of technical difficulties that still beset this class of therapeutics will ensure that protein-based products will overwhelmingly predominate for the foreseeable future. Many of the initial biopharmaceuticals approved were simple replacement proteins (e.g. blood factors and human insulin). The ability to alter the amino acid sequence of a protein logically coupled to an increased understanding of the relationship between protein structure and function has facilitated the more recent introduction of several engineered therapeutic proteins. So far, most of the approved recombinant proteins have been produced in the bacterium E. coli, the yeast S. cerevisiae or in animal cell lines (most notably Chinese hamster ovary (CHO) cells or baby hamster kidney (BHK) cells. Although most biopharmaceuticals approved to date are intended for human use, a number of products destined for veterinary application have also come on the market. One early such example is that of recombinant bovine GH (Somatotrophin), which was approved in the USA in the early 1990s and used to increase milk yields from dairy cattle.

Protein structure, Gene Manipulation and Drug development process

Proteins are macromolecules consisting of one or more polypeptides. Making up each polypeptide are chains of amino acids linked together by peptide (amide) bonds. The exact amino acid sequence is determined by the gene coding for that specific polypeptide. When synthesized, a polypeptide chain folds up, assuming a specific three-dimensional conformation that is unique to it. This shape is dependent on the polypeptide’s amino acid sequence and is stabilized by multiple, weak non-

covalent bonds. Any influence (e.g. certain chemicals and heat) that disrupts such weak interactions results in disruption of the polypeptide's native conformation, a process termed denaturation. This usually results in loss of functional activity, clearly demonstrating the dependence of protein function on protein structure. A protein's structure currently cannot be predicted solely from its amino acid sequence. Its conformation can, however, be determined by techniques such as X-ray diffraction and nuclear magnetic resonance (NMR) spectroscopy.

Proteins are sometimes classified as 'simple' or 'conjugated'. Simple proteins consist exclusively of polypeptide chain(s) with no additional chemical components present or being required for biological activity. Conjugated proteins, in addition to their polypeptide components(s), contain one or more non-polypeptide constituents known as prosthetic group(s). The most common prosthetic groups found in association with proteins include carbohydrates (glycoproteins), phosphate groups (phosphoproteins), vitamin derivatives (e.g. flavoproteins) and metal ions (metalloproteins).

The biopharmaceutical sector is largely based upon the application of techniques of molecular biology and genetic engineering for the manipulation and production of therapeutic macromolecules. The majority of approved biopharmaceuticals are proteins produced in engineered cell lines by recombinant means. Examples include the production of insulin in recombinant E. coli and recombinant S. cerevisiae, as well as the production of EPO in an engineered (Chinese hamster ovary) animal cell line. Terms such as 'molecular biology', 'genetic engineering' and 'recombinant DNA (rDNA) technology' are sometimes used

interchangeably and often mean slightly different things to different people. Molecular biology, in its broadest sense, describes the study of biology at a molecular level, but focuses in particular upon the structure, function and interaction/relationship between DNA, RNA and proteins. Genetic engineering, on the other hand, describes the process of manipulating genes (outside of a cell's/organism's normal reproductive process). It generally involves the isolation, manipulation and subsequent reintroduction of stretches of DNA into cells and is usually undertaken in order to confer on the recipient cell the ability to produce a specific protein, such as a biopharmaceutical. 'rDNA technology' is a term used interchangeably with 'genetic engineering'. rDNA is a piece of DNA artificially created in vitro which contains DNA (natural or synthetic) obtained from two or more sources.

Basic approach to cloning of gene segment

a) Initial enzyme-based fragmentation of intact genomic DNA, so that it is broken down into manageable fragment sizes for further manipulation. Ideally all/most fragments will contain one gene.

b) Integration of the various fragments generated into cloning vectors, which are themselves small DNA molecules capable of self-replication. Typically, these are plasmids or viral DNAs and the composite or engineered DNA molecules generated are called rDNA.

c) Introduction of the vectors housing the DNA fragments into host cells.

d) Growing these cells on agar plates.

e) Screening/identification of the host cell colonies containing the rDNA molecules (i.e. screening the ‘library’ of clones generated) in order to identify the specific colony containing the target DNA fragment, i.e. the target gene.

The Pharmaceutical industry adopts several strategies in their efforts to identify new drug products. These approaches range from random screening of a wide range of biological materials to knowledge-based drug identification. Once a potential new molecule has been identified, it is then screened (both in vitro and in animals) in order to characterize its safety and effectiveness in treating its target disease. The manufacturer will also undertake manufacturing related development work (development and initial optimization of upstream and downstream processing), as well as investigating suitable potential routes of product administration. After completing such preclinical trials, the developing companies apply to the appropriate government-appointed agency, e.g. NAFDAC in Nigeria, the Food and Drug Administration (FDA) in the USA, for approval to commence clinical trials (i.e. to test the drug in humans). Clinical trials are required to prove that the drug is safe and effective when administered to human patients, and these trials may take 5 years or more to complete. Once the drug has been characterized, and perhaps early clinical work is underway, the drug is normally patented by the developing company in order to ensure that it receives maximal commercial benefit from the discovery. Upon completion of clinical trials, the developing company collates all the preclinical and

clinical data they have generated, as well as additional pertinent information, e.g. details of the exact production process used to make the drug. They submit this information as a dossier (a multivolume work) to the regulatory authorities. Regulatory scientific officers then access the information provided and decide (largely on criteria of drug safety and efficacy) whether the drug should be approved for general medical use. If marketing approval is granted, the company can sell the product from then on. As the drug has been patented, they will have no competition for a number of years at least. However, in order to sell the product, a manufacturing facility is required, and the company will also have to gain manufacturing approval from the regulatory authorities. In order to gain a manufacturing licence, regulatory inspectors will review the proposed manufacturing facility. The regulatory authority will only grant the company a manufacturing licence if they are satisfied that every aspect of the manufacturing process is conducive to producing a safe and effective product consistently.

Examples;

1. **Cytokines**; are a diverse group of regulatory proteins or glycoproteins whose classification remains somewhat diffuse. These molecules are normally produced in minute quantities by the body. They act as chemical communicators between various cells, inducing their effect by binding to specific cell surface receptors, thereby triggering various intracellular signal transduction events. For example,

- The interleukins (IL-1 to IL-33)
- The interferons (IFN-α, -β, -γ, -τ, -ω)
- CSFs (G-CSF, M-CSF, GM-CSF)
- TNFs (TNF-α, -β)
- The neurotrophins (NGF, brain-derived neurotrophic factor (BDNF), NT-3, NT-4/5)
- Ciliary neurotrophic factor (CNTF)
- Glial cell-derived neurotrophic factor (GDNF)
- EGF
- EPO
- Fibroblast growth factor (FGF)
- Leukaemia inhibitory factor (LIF)
- Macrophage inflammatory proteins (MIP-1α, -1β, -2)
- PDGF
- Transforming growth factors (TGF-α, -β)
- TPO

Owing to their biological activities most interferons are of actual or likely use in the treatment of many medical conditions, including:

a. augmentation of the immune response against infectious agents (viral, bacterial, protozoal, etc.);

b. treatment of some autoimmune conditions;

c. treatment of certain cancer types.

2. **Growth factors**; The ability of growth factors to promote accelerated cellular growth, differentiation and/or division has predictably attracted the attention of the pharmaceutical industry. Several such products, most notably a range of haematopoietic growth factors, have now gained approval for general medical use.

3. **Therapeutic hormones;** endocrine hormones, remain a fairly well defined group. Virtually all of the hormones used therapeutically fit into this grouping. Examples include insulin, glucagon, GH and the gonadotrophins.

   Blood and blood products constitute a major group of traditional biologics. The main components of blood are the red and white blood cells, along with platelets and the plasma in which these cellular elements are suspended. Whole blood remains in routine therapeutic use, as do red blood cell and platelet concentrates. A variety of therapeutically important blood

proteins also continue to be purified from plasma. These include various clotting factors and immunoglobulins. However, in keeping with the scope of this book, we focus in this chapter upon blood proteins/blood-related proteins produced by genetic engineering. These include recombinant coagulation factors, anticoagulants (such as hirudin) and thrombolytics (such as tPA). Enzymes of therapeutic value include asparaginase (anti-cancer), urokinase (thrombolytic agent), nuclease (cysticnfibrosis), superoxide dismutase (Oxygen toxicity), lactase (digestive aid) etc.

Product	**Indication**	**Company**
Neupogen (filgrastim; G-CSF)	Neutropenia caused by chemotherapy Bone marrow transplants	Amgen Inc.
Leukine (sargramostim, GM-CSF)	Autologous bone marrow transplantation Neutrophil recovery after bone marrow transplantation	Berlex Labs
Neulasta (PEGylated fi lgrastim, see above)	Neutropenia	Amgen
Epogen (epoetin alfa, rEPO)	Anaemia associated with various medical conditions	Amgen
Procrit (epoetin alfa, rEPO)	Anaemia associated with various medical conditions	Ortho Biotech

Neorecormon (epoetin beta, rEPO)	Anaemia associated with various medical conditions	Boehringer-Mannheim
Aranesp (darbepoetin alfa, a rEPO analogue)	Anaemia associated with various medical conditions	Amgen
Nespo (darbepoetin alfa, a rEPO analogue	Anaemia associated with various medical conditions	Dompe Biotec
GEM 21S (implantable product containing rhPDGF-BB)	Periodontally related defects	Luitpold Pharmaceuticals and Biomimetic Pharmaceuticals
Iplex (mecasermin rinfabate, complex of rhIGF-1 and IGFBP-3)	Growth failure in children	Insmed
Regranex (becaplermin, rPDGF)	Neuropathic diabetic ulcers	Janssen & Ortho-McNeil
Kepivance (palifermin, rKGF)	Severe oral mucositis	Amgen
Increlex (mecasermin, rh IGF-1)	Growth failure in children	Tercica/Baxter

PHARMACOGENOMICS

What is Pharmacogenomics?

Pharmacogenomics is the study of genetic variations that influence individual response to drugs. Knowing whether a patient carries any of these genetic variations can help prescribers individualize drug therapy, help pharmacists reduce the potential for adverse drug events, and increase the effectiveness of drugs. Pharmacogenomics is the study of how genes affect a person's response to drugs. This relatively new field combines pharmacology (the science of drugs) and genomics (the study of genes and their functions) to develop effective, safe medications and doses that will be tailored to a

person’s genetic makeup. The most common variations in the human genome are called single nucleotide polymorphisms (SNPs). There is estimated to be approximately 11 million SNPs in the human population, with an average of one every 1,300 base pairs. An individual's response to a drug is often linked to these common DNA variations. In a similar manner, susceptibility to certain diseases is also influenced by common DNA variations. Currently, much of the research in the field of pharmacogenomics is focused on genes encoding either metabolic enzymes that can alter a drug's activity or defective structural proteins that result in increased susceptibility to disease.

Anticipated benefits of Pharmacogenomics

Pharmacogenomics has the potential to provide tailored drug therapy based on genetically determined variation in effectiveness and side effects. This will mean:

•More powerful medicines - Pharmaceutical companies will be able to produce therapies more targeted to specific diseases, maximizing therapeutic effects while decreasing damage to nearby healthy cells.

•Better, safer drugs the first time - Recovery time will go down and safety will go up as the likelihood of adverse reactions goes down or is eliminated altogether.

•More accurate methods of determining appropriate drug dosages - Current methods of basing dosages on weight and age will be replaced with dosages based on a person's genetics --how well the body processes the medicine and the time it takes to metabolize it.

Practical applications of pharmacogenomics today

1. In a clinical trial involving 1536 patients, two common and tightly linked SNPs were significantly associated with reduced efficacy of pravastatin therapy. Both of these SNPs were in the gene coding for 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the target enzyme that is inhibited by pravastatin. For example, compared with individuals homozygous for the major allele of one of the SNPs, individuals with a single copy of the minor allele had a 22% smaller reduction in total cholesterol.

2. Studies to elucidate the influence of genetic processes on Selective Serotonin Re-uptake Inhibitor efficacy now represent a major focus of pharmacogenomics research. Current evidence emerging from the field suggests that gene variants within the serotonin transporter and cytochrome P450 drug-metabolising enzymes may bear a particular importance, though further corroboration of these findings is still warranted.

At the same time, it appears likely that further key participating genes remain to be identified. By comprehensively delineating these genetic components, it is envisaged that this will eventually facilitate the development of highly sensitive protocols for individualizing SSRI treatment.

REFERENCES

Rapid Response, WHO (2011). Guidelines for Medicine Donations.

Ogbonnan BO, Ilika AL and Nwabueze A (2015). National Drug Policy 1985-2015. WJPR 4(6):248-264

Walsh G (2007). Pharmaceutical Biotechnology: concepts and applications. John Wiley & sons, England.