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Pharmacy and Pharmacology

Similarities & Differences

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Pharmacy and Pharmacology Similarities & Differences

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Part I: Pharmacy

Introduction to pharmacy

Most people including health professionals confuse pharmacology and pharmacy. While pharmacology is one of the specialties/branches of pharmacy, pharmacy is the third largest profession in the globe after nursing and medicine. Pharmacy is as old as human age. Pharmacy is responsible for provision of pharmaceutical care. It is represented internationally by international pharmacy federation (FIP). The word pharmacy is derived from Old French farmacie "substance, such as a food or in the form of a medicine which has a laxative effect", from Medieval Latin pharmacia, from Greek pharmakeia "a medicine", which itself was derived from pharmakon, meaning "drug, poison" (which is etymologically related to pharmakos). Apothek is the old name for pharmacy [1,2].

Professionals who practice pharmacy are called pharmacists. Apothecary is the old name for pharmacists. There are mid-level professionals known as pharmacy technicians/druggists, who support pharmacists. Pharmacists can practice in health care institutions (hospital, health center, clinics), pharmaceutical industry, academia, research institutions, regulatory agencies, drug suppliers, drug distributors, drug wholesalers, drug retail outlets (community pharmacy, drug stores), consultancies and non-governmental organizations. Pharmacy practice is regulated by federal ministry of health and its agencies (Ethiopian Food and Drug Administration, Ethiopian Pharmaceutical Supplies Agency, Ethiopian Pharmaceutical Funds Agency). Federal ministry of trade and industry as well as federal ministry of innovation and technology also take part in the same [3].

The practice of pharmacy has changed from product oriented one to clinical oriented one in Ethiopia, following curricular paradigm shift. Pharmacy education is governed by schools of pharmacy consortium and federal ministry of science and higher education. Currently, there are over 10 schools of pharmacy in Ethiopia. Today, pharmacy is provided from midlevel to terminal doctoral degree level in Ethiopia. Pharmacists can thus, specialize in pharmacology, toxicology, pharmacotherapy, pharmaceutics, pharmacognosy, pharmaceutical analysis, pharmaceutical quality control and assurance, medicinal chemistry, complementary and alternative medicine, pharmacoepidemiology, pharmacoeconomics, pharmaceutical supply chain system, pharmacy administration and others [3,4].

Ethiopian pharmacists are legally represented by "Ethiopian Pharmaceutical Association".

History of pharmacy

The origin of pharmacy

Before the Dawn of History from beginnings as remote and simple as these came the proud profession of Pharmacy. The profession of pharmacy did not exist alone, it was integrated with medicine. Its development parallels that of man. Babylon, jewel of ancient Mesopotamia, often called the cradle of civilization, provides the earliest known record of practice of the art of the apothecary. Practitioners of healing of this era (about 2600 B.C.) were priest, pharmacist and physician, all in one. Shen Nung (China, about 2000 B.C)examined many herbs, barks, and roots brought in from the fields, swamps, and woods that are still recognized in Pharmacy today. Medicinal plants include podophyllum, rhubarb, ginseng, stramonium, cinnamon bark, and, in the boy's hand, ma huang, or Ephedra. Egyptian medicine dates from about 2900 B.C., and best known for its pharmaceutical record "Papyrus Ebers" (successfully compiled by 1500 B.C), a collection of 800 prescriptions, mentioning 700 drugs. Theophrastus (about 300 B.C.) in Greek, King of Pontus (about 100 B.C.) and Terra Sigillata(500 B.C) were critical players in ancient pharmacy. Dioscorides, Galen and, Damian and Cosmas (the twins), and Ibn Sina had laid foundation for modern pharmacy. Until these times, pharmacy and medicine was not separated [1,2,4].

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The separation of medicine and pharmacy

The Arabs separated the arts of apothecary and physician, establishing in Bagdad late in the eighth century the first privately owned drug stores. When the arabs swept across Africa, Spain and southern France, they carried with them a new pattern of Pharmacy which western Europe soon assimilated. In European countries exposed to Arabian influence, public pharmacies began to appear in the 17th century. However, it was not until about 1240 A.D. that, in Sicily and southern Italy, Pharmacy was separated from Medicine. Frederick II of Hohenstaufen, who was Emperor of Germany as well as King of Sicily, was a living link between Oriental and Occidental worlds. At his palace in Palermo, he presented subject Pharmacists with the first European edict completely separating their responsibilities from those of Medicine, and prescribing regulations for their professional practice. The idea of a pharmacopoeia with official status, to be followed by all apothecaries, originated in Florence. The Nuovo Receptario, originally written in Italian, was published and became the legal standard for the city-state in 1498. It was the result of collaboration of the Guild of Apothecaries and the Medical Society - one of the earliest manifestations of constructive interprofessional relations. The professional groups received official advice and guidance from the powerful Dominican monk, Savonarola, (seated, foreground) who, at the time, was the political leader in Florence [4,5].

Pharmacy as a full pledge profession

The Society of Apothecaries and organization of pharmacists were established in the Anglo-Saxon world. Canada and USA followed the footsteps of British. The first Hospital Pharmacy began operations in USA in 1752. John Morgan, whose practice as a hospital pharmacist (1755-56), and whose impact upon Pharmacy and Medicine influenced changes that were to become of importance to the development of professional pharmacy in North America. First as pharmacist, later as physician, he advocated prescription writing and championed independent practice of two professions [6,7].

Important discoveries by pharmacists

The pharmacist Carl Wilhelm Scheele had made many important discoveries in the Sweden. He discovered oxygen, chlorine, prussic acid, tartaric acid, tungsten, molybdenum, glycerin, nitroglycerin, and countless other organic compounds that enter into today's daily life, industry, health, and comfort. The German Friedrich Wilhelm Adam Sertürner discovered morphine. Pierre-Joseph Pelletier and Joseph-Bienaimé Caventou, isolated emetine from ipecacuanha in 1817; strychnine and brucine from nux vomica in 1818; quinine and cinchonine from the cinchona barks in 1820 [8,9].

Pharmaceutical manufacturing

Pharmaceutical manufacturing as an industry apart from retail Pharmacy had its beginnings about 1600; really got under way in the middle 1700's. It developed first in Germany, then in England and in France. In America, it started late. Utilizing latest technical advances from every branch of science, manufacturing Pharmacy economically develops and produces the latest and greatest in drugs in immense quantities, so that everywhere physicians may prescribe them and pharmacists dispense them for the benefit of all mankind [10-13].

Important developments

American pharmacists established an association and first educational institution 1821. Shaker, first U.S. industry in medicinal herbs became commercially important by 1830. The American Pharmaceutical Association established in 1852, the Association that continues to serve Pharmacy today. The first "United

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States Pharmacopoeia" (1820) was the work of the medical profession. In 1877, pharmacists formed a "Committee on Revision" chaired by hospital pharmacist Charles Rice, assisted by pharmacist-educator Joseph P. Remington, and by Dr. Squibb, their indefatigable collaborator. The "U.S. Pharmacopoeia" surged to new importance. The Standardization of Pharmaceuticals started in 1883 by Parke-Davis. Parke-Davis also pioneered in developing pharmacologic and physiologic standards for pharmaceuticals. Today, the American pharmacy education is completely changed to pure clinical pharmacy. The first professional degree program is doctor of pharmacy (Pharm. D) program. There is no Bachelor of Pharmacy (B.Pharm) program since 2000 [3,14-17].

Currently the USA has over 140 schools/Colleges of pharmacy. India has over 130, China, Bangladesh, Turkey, Pakistan have over 30 schools of pharmacy; Brazil, France, Germany, Italy, Japan, Philippines, South Korea and UK have over 20 schools of Pharmacy. In Africa, Egypt leads by over 25 schools of pharmacy, and Ethiopia follows by over 15 schools of pharmacy. The rest have less than 10 schools of pharmacies.

However, the number of schools alone does not dictate the status of pharmacy education and practice in a given country. The quality also matters.

History of pharmacy in Ethiopia

Pharmacy practice: In Ethiopia, the concept of pharmacy practice was thought to exist at the time of king Libnedingil (1520-1526). The historical account in the southern part is lacking. However, this does not mean that it did not exist. Travelers from western world to Ethiopia, whether they are health professionals or not, were considered at time as healers, since they used to bring extra drugs for the community. The establishment of retail outlets of modern drug products however took the stage at considerably latter times during the reign of king Minilik II (1889-1913). Until the eve of the Italian occupation in 1935, very few such modern drug retail outlets had been operational only in some parts of the capital Addis Ababa; notably around and dedicated to the inner circles of the royal families. Most of the owners of these early drug retail outlets were foreigners and Pharmacie La Georgie, owned by Dr Mareb, a Georgian and one of the private Doctors of the King, is historically credited as the first modern Pharmacy opened in Ethiopia. There were however court Pharmacies up in the Palace of King Minilik II before they were opened in the downtown of the then flourishing Addis Ababa. After the end of the brief Italian occupation that lasted for some five years, all the foreign-owned pharmacies were confiscated by the then government of Ethiopia and some Italians were employed to work in these Pharmacies afterwards. Currently, drug distribution and retailing activities in Ethiopia are carried out by a combination of public sector, private sector, city councils, the Ethiopian Red Cross Society (ERCS) and even other NGOs. Pharmacy services have now advanced and include clinical pharmacy services and drug information centers. Besides, the traditional supply and dispensing of drugs have improved with supplementation of technological packages and participation of NGOs in the sector. However, compared to the global status, pharmacy service in Ethiopia is still decades away; and even the clinical pharmacy service is staggering, as the enforcement frame is either weak or absent [3,18].

Pharmacy education*:* The first auxiliary medical training in Ethiopia was launched by the then Ministry of Interior in Minilik II hospital in 1943 in which some 12 students are known to had been enrolled 4. The requirements for entrance has never been clear but the students enrolled had some ability of foreign languages and those completed (only 4) were awarded "Hospital Dispensary Certificates" . Few other attempts were also made then after, which took a bit longer time to complete and had a clearly known entrance requirements. The 1947 one year long training coordinated by the then Imperial Medical Research Institute can be the case in point. In this training, students were required to complete 6th grade and also pass an English entrance exam. Basic sciences and some Pharmacy courses were given to the 11 students admitted to the program who were awarded a "Pharmacy Assistant Certificate" after completion. All the courses were offered by only one Swedish man who was a diploma holder in the field [18].

The Ethiopianization of the modern Pharmaceutical education was however heralded by the establishment of a Pharmacy Technicians School in the compound of the Current Minilik II hospital. Completion of 9th grade was the requirement for entrance and the school thought all the important Pharmacy and other basic sciences courses like Physiology for two years. The first School of Pharmacy was established in September 1961 as a unit under the Faculty of Science of the then Haile-Selassie I University with the goal of producing pharmacists to handle the country's pharmaceutical and health needs. In 1978, the Department of Pharmacy was raised to a full-fledged Faculty status under the name of "School of Pharmacy" and stayed as such until 2010. Following the reorganization of the Addis Ababa University, it joined three other Schools and Tikur Anbessa Hospital to form the College of Health Sciences. School of Pharmacy currently provides training from bachelor to terminal doctoral level. The second School of Pharmacy was established in September 1985 under the auspices of the former Jimma Institute of Health Sciences, later promoted to Jimma University, with the aim of the training to produce mid-level pharmacy professionals, who will take part in teaching the community in proper use of drugs and render pharmaceutical services. Since September 2001, the

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school commences training of pharmacists at Bachelor Degree level in both regular, extension and summer programs of the University. The third school of Pharmacy was established under University of Gondar in 2001. The fourth was established under Mekelle University in 2004. Then, followed Haramaya University, Wollega University and Wollo University in 2007. Currently, over 15 public universities and around 5 private universities do provide bachelor of pharmacy program in regular and extension classes. Mekelle University has gone half ways to launch a 3-4 years post-baccalaureate Pharm.D program. The outcome will be evaluated in the coming few years. School of Pharmacies in Ethiopia have established the consortium of the -school of pharmacies on December 26, 2016. All public schools of pharmacies in Ethiopia and few private colleges are members. The objective of establishing the consortium is to bring the schools of pharmacy under one umbrella in such a way that they can regularly meet and review the pros and cons of the current pharmacy education/training in Ethiopia and work to rectify the limitations [3,18].

The major criticism regarding pharmacy education in Ethiopia is that, much focus is given to theoretical components than practical components. This is due to lack of facilities and weak linkages with industries. Thus, to raise the quality of education, proportionate focus must be given for practical training and soft skill development, and the training of highly skilled specialists that a modern industrial sector needs must be in place.

Professional association

Ethiopian pharmacists are represented national by Ethiopian Pharmaceutical Association (EPA).

EPA was established in 1974 and it is a National Association of pharmacists in the Federal Democratic Republic of Ethiopia working to uphold the honor and ethics of the profession, safeguarding members' professional rights and working with relevant stakeholders to ensure that the public gets quality pharmaceutical products and services in Ethiopia. EPA aspires to advance the health and well-being of the society and to become one of the leading professional associations in Ethiopia, a model in Africa and globally respected. EPA is working with Federal Ministry of Health of Ethiopia (FMoH) and its partners, Ministry of industry and its partners, consortium of the school of pharmacies and international Pharmaceutical Federation (FIP) [19,20].

Research and development

Pharmacy Research is at its infancy in Ethiopia. Molecular researches are unthinkable due to lack of facilities. Clinical researches are only recently emerging with the beginning of clinical pharmacy and clinical pharmacology programs. Center of excellence is lacking. There is an old drug research department established under Ethiopian Public health Research Institute (EPHI, popularly known as 'Pasteur'), one of the agencies of FMoH. The department mainly focuses on herbal medicines, although no product has ever reached market from this department. Jimma University has recently established a standard drug quality laboratory in collaboration with Ghent University. This lab has best facility, run by experts and easily accessible. Besides, school of pharmacies conduct research as part of requirements of graduation for both undergraduate and post graduate programs. Staffs from these schools also conduct thematic researches in collaboration with pharmaceutical industries, NGOs and research institutions. Researches must be disseminated as well. Accordingly, EPA has established Ethiopian Pharmaceutical Journal (EPJ) for such purposes. EPJ is a biannual Journal, which publishes original research works that contribute significantly to further scientific knowledge in Pharmaceutical Sciences. The Journal publishes original research work either as a Full research Paper or as a Short Communication. It was indexed since 2004(volume 22) and is currently in its volume 36. It available online and can be accessed on African Journals Online (AJOL) [3,18].

Pharmacy today and tomorrow

Pharmacy, with its heritage of 50 centuries of service to mankind, has come to be recognized as of the great professions. Pharmacists are among the community's finest educated people. Today both pharmacy education and practice has shifted from product oriented to clinical oriented one. That does not mean that the traditional role pharmacy would be obsolete. Rather a clinical oriented practice takes the full responsibility of all aspects of pharmacy, from manufacturing of quality drugs to the proper use of the drugs by patient, including affordability and accessibility. Additionally, pharmacists are assuming key roles in health promotion, disease prevention and the management of systems and resources associated with health care delivery. Such responsible provision of pharmaceutical services is called pharmaceutical care. Pharmaceutical care will go to advanced level by using pharmacometrics and pharmacogenetics. We shall see tomorrow's pharmacist at the heart of advanced clinical decision makings, including prescriptive authority. In line with these, the curricula should be as dynamic as the rapid practice changes demanded. Although decades away from the rest of the world with regard to practice, Ethiopian pharmacy education is at least at the same level of understanding with the world. That is why Ethiopian pharmacists got easy working in USA, where the latest standard in pharmacy practice and education is benchmarked [3].

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Pharmacy symbols

Snake and bowl: The history of the symbol of pharmacy is diverse and is one which shares its beginning in many ancient cultures throughout the world and snakes or serpents have been a common occurrence in mythology throughout history. Snakes have been used for worship, magic potions and, medicine, and they have been the symbol of love, health, disease, medicine, pharmacy, immortality, death, and even wisdom since ancient times.

According to the Greek myths, Asclepius (Asklepios), the Greek God of medicine learned the art of healing from both his father Apollo and the centaur Cheiron. In time, he became so skilled in surgery and the use of drugs that he was revered as the founder of medicine. A major sanctuary was dedicated to him at Epidaurus, the place where he was born. It was believed that Asclepius had the power to rise from the dead. Legend tells that Zeus was worried that Asclepius would make mankind immortal because of his healing power. Out of fear, Zeus killed him with a lightning bolt. Temples were built for Asclepius, and seemingly dead serpents were found inside. When these serpents were picked up and dropped, however, they slithered away. To people, this was interpreted as that the serpents were brought back to life by the healing powers of Asclepius, which ultimately caused them to be associated with healing. Tame snakes were kept in his temples as this animal was regarded as a symbol of regeneration [21-23].

From about 300 B.C. onwards, the cult of Asclepius grew very popular and pilgrims flocked to his healing temples (Asclepieia) to be cured of their ills. The Rod of Asclepius, also known as the Staff of Asclepius, a serpent-entwined rod wielded by the Greek god Asclepius is today associated with medicine and health care. The serpent and the staff appear to have been separate symbols that were combined at some point in the development of the Asclepian cult.

According to university of Arizona Health Sciences, in Greek mythology, Hygeia was the daughter and assistant of Asclepius, the son of Apollo, grandson of Zeus, and the god of medicine and healing. Interestingly, this same serpent is found on the so-called Staff of Aesculapius and on the Caduceus, both widely recognizable symbols of medicine. The serpent of Epidaurus hugging a cup appears, from 1222, in apothecaries of Padua (Italy) as a distinctive symbol of the pharmacy used as the main pattern of their banner. The serpent symbolizes the healing art, fertility and life.

The significance of the serpent has been interpreted in many ways; sometimes the shedding of skin and renewal is emphasized as symbolizing rejuvenation, while other assessments center on the serpent as a symbol that unites and expresses the dual nature of the work of the Apothecary Physician, who deals with life and death, sickness and health. The snake also represents the mixed interpretations of medicines as medicines or as poisons which also appertains to the Greek word 'Pharmakon', meaning a drug or a poison. Products deriving from the bodies of snakes were known to have medicinal properties in ancient times, and in ancient Greece, at least some were aware that snake venom that might be fatal if it entered the bloodstream could often be imbibed. Snake venom appears to have been 'prescribed' in some cases as a form of therapy. Snakes represented the devil in the Abrahamic Garden of Eden, in the story of Moses, his staff transmogrified into a snake and in the Christian Bible, a bronze serpent-shaped staff was crafted by Moses and anyone bitten by a snake, who looked upon it would live.

Today the symbol of the rod and snake or bowl and snake (Figure 1), as used through the world in various healthcare organizations. The World Health Organization has a rod of Asclepius in its center, and various medical organizations throughout the world employ this symbol. It is also the primary symbol of pharmacy in Europe and the Middle-east. These symbols are also commonly mixed with the words Rx which itself is believed to be derived from the Eye of Horus and the Latin word for recipe. These symbols also reflect the co-existence of pharmacy and medicine since man's age [2,21-23].

Figure 1: Bowl and snake.
Legend: The bowl of Hygieia has been used as a symbol of the pharmacy profession at least as far back as 1796, when it was used on a coin minted for the Parisian Society of Pharmacy. It has since been adopted by many more pharmaceutical associations worldwide.

The international pharmaceutical federation, Ethiopian Pharmaceutical Association (Figure 2) and many community pharmacies in Ethiopia also use the snake and the bowl as their symbol or logo.

Mortar and pestle with the Rx symbol

This symbol is widely used in the Anglo-Saxon culture. It refers to a medical prescription but is also used as a symbol of pharmacy. Rx is an abbreviation of prescription, from the Latin recipe, it means «recipe take thou» which means "take it in the name of god". It also symbolizes the prayer to the God of medicine, Jupiter. The mortar and pestle (Figure 3) are two tools used since ancient times by the apothecaries and pharmacy technicians to grind various products of the pharmacopoeia for pharmaceutical preparations and compounded products. It is one of the most frequent symbols of

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Figure 2: Logos of Ethiopian Pharmaceutical Association and International Pharmaceutical federation.
Legend: The logos of Ethiopian Pharmaceutical Association and international pharmaceutical association that is created by incorporating the bowl and snake symbol.

Figure 3: Mortar and Pestle.
Legend: Mortar and pestle is a set of two simple tools used from the Stone Age to the present day to prepare ingredients or substances by crushing and grinding them into a fine paste or powder in the kitchen, laboratory, and pharmacy. It is sill used as one of the symbols of Pharmacy.

compounding worldwide [2].

This symbol is familiar in Ethiopia, special in association with compounding practices.

Green cross

The cross is the symbol of rescue and of military and civil protection. This cross, also called the "Greek cross", has four equal arms and it has become a symbol of Christianity over time. Originally this famous cross was red. The pharmacists borrowed this symbol from the international organization of the Red Cross, an organization created in the late 19th century.

The emblem had been adopted by many pharmaceutical manufacturers who added it to their packaging. Pharmacists followed the movement by making their emblem of this Red Cross. However, in 1913, the Geneva Convention prohibited the use of the Red Cross to pharmacists who, finally, adopted the green cross [2].

Some people mention the vegetal origin of many medications; others evoke the World War I as to why the cross is green. Indeed, at that time, doctors and pharmacists had to have the same uniform as officers, the only variable being the badges on the collar. It was then decided that doctors had to wear a crimson velvet collar and pharmacists a dark green collar. This symbol is used in USA, France, Belgium, Ireland, Italy, Spain, Argentina, India and many other countries (Figure 4).

Figure 4: Green cross used as symbol of pharmacy.
Legend: The cross is a reference to the 'Croix-Rouge', the international humanitarian movement and the green color simply makes a link to the plants that are used as source of drugs.

The red stylized letter A

This symbol is used by all pharmacies in Austria and Germany. It is also sometimes found in their European neighboring countries [2]. This Gothic letter A on white background is just the first letter of the word "Apotheke" or "Apotheker" synonym of Pharmacy and Pharmacist respectively (Figure 5).

Figure 5: The capital letter "A" used to symbolize aopthek.
Legend: The capital Gothic letter A and the snake or cross holy have been designated as the official logo of the pharmacy profession in some European countries like Germany.

Scope of pharmacy practice and education

The scope of pharmacy practice includes more traditional roles such as manufacturing/ compounding and dispensing of medications, as well as more modern services related to health care, including clinical services, supply chain management (assuring availability of quality drugs), reviewing medications for safety and efficacy, and providing drug information. The practice of pharmacy requires excellent knowledge of drugs, biological systems and pathological processes. Some specialties of pharmacy, such as clinical pharmacy, require other skills, e.g. knowledge about the acquisition and evaluation of physical and laboratory data. The profession of pharmacy is founded on biomedical sciences (e.g. physiology, pathology, anatomy, biochemistry, microbiology, Parasitology etc.), pharmaceutical sciences (e.g. pharmacology, Toxicology, Pharmacognosy, chemistry of natural products, pharmaceutics, biopharmaceutics, Pharmaceutical Analysis, Medicinal Chemistry), clinical sciences/practices (pharmacotherapeutics, drug informatics, clinical pharmacy clerkship), and social pharmacy courses (e.g. Drug supply management,

Pharmacoeconomics, pharmacoepidemiology) [3,27].

The professional courses can be thoughtfully grouped under six departments

Pharmacology: Pharmacology, toxicology, pharmacogenomics etc. Pharmacology studies the interaction of drugs with living organisms or tissues. Pharmacology is the bridge that links pharmacy with other health professions. Pharmacology is provided to almost all health professions, such as pharmacy, medicine, public health/Health Officer, nursing, midwifery, anesthesia, medical laboratory science/technology and biomedical sciences. Accordingly, pharmacology plays ambassadorial roles for pharmacy profession.

Pharmacognosy: *Pharmacognosy, Chemistry of natural products (CNP), Complementary and alternative medicine (CAM)* etc. Pharmacognosy is generally about the study of the physical, chemical, biochemical, and biological properties of drugs, drug substances, or potential drugs or drug substances of natural origin as well as the search for new drugs from natural sources.

Pharmaceutics: Pharmaceutics, physical pharmacy, biopharmaceutics, pharmacokinetics, industrial pharmacy, immunological and biological products etc. Pharmaceutics generally deals with all facets of the process of turning a new chemical entity (NCE) into a safe and effective medication. It is the science of formulation/dosage form design. It blends physical chemistry, biology and pharmaceutical sciences to come up with safe and effective formulation/dosage form.

Pharmaceutical chemistry: Medicinal chemistry, pharmaceutical analysis and quality assurance/quality control etc. Pharmaceutical chemistry deals with design, synthesis, structure-active-relationship (SAR), modification, quality control and assurance of drugs. It blends bioinformatics, organic chemistry and analytical chemistry with pharmaceutical sciences.

Clinical pharmacy: Pharmacotherapy, drug informatics, clinical pharmacy clerkships etc. Clinical pharmacy is the branch of pharmacy in which clinical pharmacists provide direct patient care that optimizes the use of medication and promotes health, wellness, and disease prevention. In this case, care for patients is performed in all health care settings but the clinical pharmacy movement initially began inside hospitals and clinics. Clinical pharmacists often work in collaboration with other health care professionals (physicians, nurses, midwives, anesthetists, medical laboratory scientists etc.). This considered being the modern roles of pharmacists. Here, pharmacists must be well trained in pharmacotherapy to play such role. Pharmacotherapy is therapy using drugs, as distinguished from surgical therapy, radiation therapy, behavioral therapy, physical therapy, nutritional therapy or other modes. It blends the knowledge of pharmacology, pathology and clinical laboratory sciences to come up with better treatment outcomes. As pharmacotherapy specialists, pharmacists have responsibility for direct patient care, often functioning as a member of a multidisciplinary team, and acting as the primary source of drug-related information for other healthcare professionals. Thus, the current trend, both globally and nationally, is to shift the pharmacy curriculum to more clinical oriented one. This should not, by any means, undermine the traditional roles of pharmacists.

Social and administrative pharmacy: Pharmacoepidemiology, Pharmacoeconomics, drug supply management (DSM), pharmacy law and ethics etc. focus on the scientific, social and humanistic bases for understanding and influencing interactions involving patients, drugs, caregivers, and health care systems. The field integrates knowledge of pharmacy with knowledge from economics, history, sociology, anthropology, psychology, management sciences, communication, education, epidemiology, law, and ethics into evaluation in order to contribute to the safe and rational use of drugs. It can be considered to consist of all factors that influence medicine use, such as medicine-related beliefs, regulations, policy, attitudes, medicine information, ethics and behavior. This also considered as new roles of pharmacists. Clinical pharmacy requires direct interaction with patients, whereas social and administrative pharmacy demands more direct interaction with the public in terms of the provision of health information and advice on the safe and rational use of medications.

The traditional gaps between clinical pharmacy and social & administrative pharmacy are shrinking. Gradually, clinical pharmacy recognizes the need to expand its repertoire of research designs, methods, and theories in order to understand the organizations and the patients they work with. Social & administrative pharmacy needs to broaden the research activities to studying pharmacy as it is practiced in a wider context—including health care institutions. Increasingly, hospitals and communities are no longer two separate worlds.

Pharmaceutical code of conduct

The Code of Ethics sets out the principles that must be followed by pharmacist or pharmacy technician. The Code is the Society's core guidance on the conduct, practice and professional performance expected. It is designed to meet obligations. The principles of the Code are intended to guide and support the work and the decisions to be made. They also inform the general public of the standards of behavior that can be expected from the pharmacy professions. The

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Code is founded on seven principles which express the values central to the identity of the pharmacy professions. The seven principles and their supporting explanations encapsulate what it means to be registered pharmacist or pharmacy technician.

- Make the care of patients your first concern
- Exercise your professional judgment in the interests of patients and the public
- Show respect for others
- Encourage patients to participate in decisions about their care
- Develop your professional knowledge and competence
- Be honest and trustworthy
- Take responsibility for your working practices.

There is a code of practice prepared by Ethiopian Pharmaceutical Association for pharmacists practicing in Ethiopia.

Pharmacy oath

As a healthcare professional and person of integrity I will . . .

- Use my knowledge, skills and abilities to do good and actively benefit my patients.
- In all instances I will make every effort to protect my patients from harm and facilitate their health and well-being through the promotion of health and wellness.
- I will do this to serve my patient's best interests.
- I will not be motivated by ambition or gain nor will I be led astray by ego or the false desire for praise or admiration.
- I will carry out all my professional duties in a spirit of goodwill and genuine caring for my patients.
- I recognize and respect human vulnerability and honor the human in all humanity.
- I recognize that I do not know what I do not know.
- That knowledge is infinite and ever-expanding and I will continually seek to learn and develop my knowledge and skills.
- I will tend to my physical, mental and emotional well-being.
- I will honor my profession and myself and protect my professional integrity at all times.
- I will keep this promise because I am committed to my patients, society, my profession and myself and accountable to all those entrusted to my care.

Pharmacy oath has never been implemented in Ethiopia for no justifiable reasons.

The seven star pharmacists

To be effective health care team members, pharmacists need skills and attitudes enabling them to assume many different functions. The concept of seven-star pharmacist was introduced by WHO and taken by FIP in 2000 in its policy statement on good pharmacy education and practice to cover these roles.

These include:

- Care giver
- Decision maker
- Communicator
- Manager
- Lifelong learner
- Teacher and researcher
- Leader

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Pharmacist and pharmacy technician/druggist

Professionals who practice pharmacy are called Pharmacists. Pharmacists are the experts on drug therapy and are the primary health professionals who optimize the use of medication for the benefit of the patients. In some jurisdictions, pharmacists have prescriptive authority to either independently prescribe under their own authority or in collaboration with a primary care physician through an agreed upon protocol called a collaborative practice agreement. The holistic service provided by pharmacists is called pharmaceutical care. Pharmaceutical care involves taking direct responsibility for patients and their disease states, medications, and management of each to improve outcomes. Such responsibility begins from production of quality products through careful monitoring of supply chain to rational use of drugs [25,27].

The role of pharmacy education, pharmacist licensing, and continuing education vary from country to country and between regions/localities within countries. However, Pharmacists must obtain a university bachelor of Pharmacy (B.Pharm e.g. Ethiopia, Australia) degree, Master of Pharmacy (M.Pharm e.g. UK) Degree or Doctorate of Pharmacy (Pharm.D e.g. USA, Canada) degree to practice the profession of pharmacy.

Pharmacists are represented internationally by the International Pharmaceutical Federation (FIP). They are represented at the national level by professional organizations such as Ethiopian Pharmaceutical Association (EPA), the Royal Pharmaceutical Society in the UK, Pharmacy Guild of Australia (PSA), Canadian Pharmacists Association (CPhA), Indian Pharmacist Association (IPA), Pakistan Pharmacists Association (PPA), and the American Pharmacists Association (APhA).

Pharmacy technicians/druggists are middle level professionals who support the work of pharmacists by performing a variety of pharmacy-related functions, including dispensing prescription drugs and other medical devices to patients and instructing on their use. Pharmacy technicians must obtain either college diploma or level IV training from Technical and Vocation Education and training Institute (TVET).

In Ethiopia, pharmacy is licensed by pharmacists, whereas drug store is licensed by pharmacy technician/druggist.

Areas of pharmacy practice

Pharmacists are the most accessible of all health workers and as such play a key role in the delivery of health care services at all levels. They represent the third largest health care professional group in the world. The majority of pharmacists practice in communities, hospitals and other medical facilities. A smaller numbers of them are employed in the pharmaceutical industry, regulatory, academic and research institutions. In Ethiopia, the pharmaceutical sector is guided by a National Drug Policy which was developed in 1993 [25-30].

Areas of pharmacy practice include

- ***Academy and research:*** Ethiopian Pharmacists and pharmaceutical scientists engage most in Academic and research sectors, next to hospital and community pharmacy sectors. Currently, more than 15 public universities and about 5 private colleges provide pharmacy education at bachelor level. A few of them also engage in postgraduate studies (MSc, M.Pharm, and PhD). The professional doctorate degree (Doctor of Pharmacy, Pharm.D) program has not yet started in Ethiopia.

- ***Consultancy:*** Pharmaceutical consultancy is a customer-focused service, where professionals offer technical guidance on specific needs of the clients (industries, companies, associations, regulatory authorities, government agencies, academic institutions etc). These can include product development, drug supply management, clinical pharmacy, training, research, critical process reviews, project management etc. Pharmaceutical Consultancy is not at required level in Ethiopia. Only some forms of fragmented services are observed.

- ***Regulatory affairs:*** In Ethiopia, even though "The Pharmacists and Druggists Proclamation No 43/1942" was used to regulate both the professions and the facilities where they were practiced, comprehensive regulation of the pharmaceutical market was introduced in 1964 by a regulation called "Pharmacy Regulation No. 288/ 1964". This legislation formed the legal basis for official establishment of drug regulation in the history of Ethiopia, enabling the regulation of the practice of pharmacists, druggists and pharmacy technicians; manufacturing, distribution, and sale of medicines. In June 1999, a new regulation called the "Drug Administration and Control Proclamation No. 176/1999" repealed most parts of the regulation 288/1964. The law established an independent Drug Administration and Control Authority (DACA) with further mandate of setting standards of competence for licensing institutions/facilities.

- DACA was re-structured as Food, Medicine and Health Care Administration and Control Authority (EFMHACA) of Ethiopia by the "Proclamation No. 661/2009" in 2010 bearing additional responsibilities like regulation of food, health

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care personnel and settings. EFMHACA was once again changed to Ethiopian Food and Drug Administration (EFDA). EFDA is responsible for the regulation of preclinical and clinical trials; ensuring medical product safety and efficacy; and the licensing and control of the distribution of medical products including imported and exported products. Its role is changing. Proclamation 11/12.2019 was passed in early February 2019 to reflect a new focus on the regulation of food and drug products, with EFMHACA converting into EFDA. EFDA issues market approval for medical products to be made available in Ethiopian market. This includes testing of all drug imports to verify that they meet local quality standards. They also certify that local pharmaceutical products meet GMP standards, that their products are allowed in the market, and that they can bid on public tenders made by EPSA [28,30].

These changes are not far from name changing and cannot bring about significant improvements. EFDA has two major limitations. One, it is accountable to the service providing ministerial office, FMoH. It is not autonomous and thus cannot unreservedly regulate services related to drugs and foods. Second, it has no adequate expertise. Just compare it to other regulatory bodies in Africa and USA. Above all, there is great mismatch between "policy formulation" and "policy implementation" in Ethiopia, in every sector. On paper, there are most of the policies, regulations, directives and guidelines. However, there is a serious implementation gap across public institutions either because of capacity constraints or misallocation of efforts and resources. EFDA is one of those institutions. There are jack of all legislations, directives, guidelines etc., with many editions and versions, but no implementation. New versions are emerging without implementing and/or evaluating the previous ones. Leave alone others, EFDA could not effectively regulate traditional medicine, insecticides, khat and tobacco. Khat is an indigenous psychostimulant that contain the main psychoactive ingredients, cathinone and cathine. These ingredients are scheduled in USA and Europe. However, they neither scheduled, nor regulated in Ethiopia. It is not known if khat is legal or not in Ethiopia; except that anything illegal is taken as legal.

- ***Drug supply management:*** The drug supply management services in Ethiopia are governed by "Ethiopian Pharmaceuticals Supply Agency (EPSA)", NGO partners (e.g. SCMS, CHAI, UNPF etc), private importers & wholesalers. Currently, nearly 400 importers and 500 wholesalers engage in drug supply services in Ethiopia. The pharmaceutical industry of Ethiopia contributes only 15% of the total market share while 85% of pharmaceutical and medical supplies products are imported. The top 15 global pharmaceuticals exporters are Germany, Switzerland, Belgium, France, USA, Ireland, UK, Italy, the Netherlands, India, Denmark, Spain, Canada, Sweden and Austria. Ethiopia imports mainly from India, USA, France, Belgium, Korea Republic, Denmark, Switzerland, Germany, UK, Netherlands, China and Cyprus. Most major international companies have presence in Ethiopian market. Some of the leading Indian companies such as Cadila, Zydus Cadila, Cipla, Ranbaxy, Ipca Laboratories, Lupin Labs., Torrent Pharma, Alembic, Sarabhai Chemicals etc. are already actively engaged in exporting pharmaceuticals to Ethiopia.

The current EPSA was first established in 1947 with a capital of 80 million birr under the name "the main Pharmacy." The military regime then restructured "the main Pharmacy" in 1976. Organizations that carried out similar activities were merged to create a new organization called Ethiopian Pharmaceutical and Medical Supplies Corporation (EPHARMECOR) [28,30].

The main task of EPHARMECOR was to distribute human, animal and plant pharmaceuticals and medical supplies it manufactured and imported from abroad. However, the steady plunge in the corporation's capital and the subsequent weakened supply necessitated another restructuring which came during the period of the transitional government in 1994. Accordingly, the transitional government allocated a huge budget to bridge the pharmaceutical gap and restructured EPHARMECOR into a new organization called Pharmaceutical and Medical Supplies Importer and wholesale Distributor (PHARMED). PHARMED was once again re-established with reformed vision, mission and goals in 2007 under proclamation No. 553/2007 bearing the name "Pharmaceutical Fund and Supply Agency (PFSA)." PFSA is structured to sustainably supply basic pharmaceuticals used for treating the main health problems in the country along with medical equipment and to consider the purchasing capacity of the society in providing its services [30].

PFSA has once again changed its name at the beginning of the 2019 to "Ethiopian Pharmaceuticals Supply Agency (EPSA)." EPSA is the public procurement agency for local and international pharmaceuticals for the public-sector health system (public hospitals, health facilities and pharmacies) in Ethiopia. It operates a main office in Addis Ababa and more than 15 regional offices throughout the country. It operates mainly through international and local tenders to supply medicines, funded by a revolving drug fund and donor programs. EPSA is also mandated to increase to reasonably priced and quality-assured drugs. Drug prices in public pharmacies are more than 50% less than that of the price private pharmacies. Besides, there is no comprehensive health insurance system coverage of pharmaceuticals yet in Ethiopia, so consumers without insurance coverage pay heavily for drugs. EPSA also provides critical support for local producers by providing a stable source of demand. Additionally, EPSA regulated the private supply wings [30].

Despite the changes in organizational structure, naming and "goals" throughout its history, the institution's primary

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activity has always been supplying pharmaceuticals and medical equipment mainly to governmental health institutions. This organization is the most frequently abused organization regarding pharmaceutical sectors. Pharmaceuticals should not be merely considered as commodities. EPSA is governed by board of directors who have no know how of pharmaceuticals. The Board comprises of seven members including the National Bank Governor (chairman), Deputy Director General of Ethiopian Airlines, State Minister of Health, General Director of Public Procurement and Property Administration Agency, Commissioner of Customs, Director General of Maritime Logistics and Transport and Director General of the Agency. Besides, a third of the executive bodies of the organization are non-pharmacy professionals.

Industrial pharmacy: Industrial Pharmacy is a discipline which includes manufacturing, development, marketing and distribution of drug products including quality assurance of these activities. Pharmacists in Ethiopia do engage in industrial pharmacy sector.

Currently, the global pharmaceutical industry has grown from a multi-billion dollar to nearly 1.5 trillion. The top 35 biggest innovator pharma companies are Johnson & Johnson (USA), Roche (Switzerland), Sinopharm (China), Pfizer (USA), Bayer (Germany), Novartis (Switzerland), Merck & Co (USA), GlaxoSmithKline (UK), Sanofi (France), AbbVie (USA) Abott laboratories (USA), Medtronic (USA), Takeda (Japan), Bristol-Myers Squibb (USA), Thermo Fischer Scientific (USA), Astra Zeneca (UK-Sweden), Amgen (USA), Gilead Sciences (USA), Eli Lilly & Co(USA), GE Health Care(USA), Viatris (USA), Boehringger-Ingelheim (Germany), Noro Nordisk (Denmark), Merk Group (Germany), and Shanghai Pharmaceuticals Holding (China) . The top five generic drug producing companies are Teva (Israel), Mylan NV (USA), Sandoz (Germany), Sun Pharmaceuticals (India) and Lupin Pharmaceuticals (India).

Pharmaceuticals industry is one of the three industries identified by the Government of Ethiopia as potential import substituting activities (the others are chemicals and metalworking). It is a strategically important industry for improving domestic health security. Manufacturing of medicines in Ethiopia started in 1964. The history of pharmaceutical manufacturing in Ethiopia is only half a century old and it may be classified into three periods: the establishment of the Ethiopian Pharmaceutical Manufacturing company (EPHARM), the subsequent boom and crash and the later 'reform and revival' period.

The first pharmaceutical manufacturing plant in Ethiopia, EPHARM was founded in 1964 as a joint venture by the Ethiopian government and the British company, Smith & Nephew. Following the overthrow of the monarchial government by the military in December 1975, the company was nationalized. Due to the socialistic policy of the military regime, private industrial investment generally stagnated and EPHARM remained the sole producer of medicines in the country until 1993. In February 1994, EPHARM was re-established as a public share holding company and recently it was sold to a local investor.

The period 1995 to 2004 experienced the boom and crash. Ten new pharmaceutical plants were established: Asmi Industry PLC, East African Pharmaceuticals (EAP), Addis Pharmaceuticals Factory (APF), ETAB PLC, Pharmacure PLC, BioSol PLC, Life-Line PLC, Fews PLC, Sino-Ethiop Associate (Africa) PLC (SEAA) and Bethelehem PLC. However, the new factories faced daunting challenges, as there were neither policies nor regulatory mechanisms to control dumping of cheaper and substandard products. The prices of local products were not competitive. In addition, most of the new factories were poorly organized and managed. Consequently, four companies were foreclosed for failure to service their loan obligations. Others survived. Established in 1996, East African Pharmaceuticals (EAP) was one of the companies that survived the 'crash' period. EAP was an initiative of British and Sudanese nationals. At the time of writing EAP has just achieved a GMP Certificate from the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S).

Established in 1997, Addis Pharmaceuticals Factory (APF) Sh. Co. is the largest pharmaceutical manufacturing plant in Ethiopia. It is located in Adigrat, Tigray Regional State, northern Ethiopia. In 2009, it acquired a second factory located at Akaki at the outskirts of Addis Ababa, which is dedicated to the manufacturing of large-volume parenterals. Sino-Ethiop Associate (Africa) PLC (SEAA) was established in March 2001 as a joint venture between an Ethiopian company, Zaf Pharmaceuticals PLC, and two Chinese companies (China Associate Group and Dandong JINWAN Group). The 'reform and revival' period began in 2005. The Ethiopian Pharmaceutical and Medical Supplies Manufacturers Association (EPMSMA) and other key stakeholders appealed to the government for appropriate measures to be taken in support of local manufacturing. To address the crisis the local manufacturers were facing, the government created benefit packages and undertook policy reforms. This improved the business environment, resulting in some new joint ventures [31-35].

In 2007, Cadila Pharmaceuticals Ethiopia PLC (CPEL) was established by Cadila Pharmaceuticals Ltd (India) and Almeta Impex PLC (Ethiopia), owning 57% and 43% of the company, respectively. Others such as Pharmacure PLC(Ethiopian-Saudi investment), Rx Africa (Ethiopia) PLC, an Ethiopian-US joint venture, Julphar (Gulf Pharmaceutical Industries),National Veterinary Institute(located in Bishoftu) have emerged. Pharmaceutical companies in Ethiopia

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are weak in innovation. They are only engaged in production of generic products. For these, they have small R&D units to formulate generic drugs. Moreover, these companies rely on imports for the supply of machinery, equipment, raw materials and intermediate inputs. All "active ingredients" that pharmaceutical enterprises require to produce medicines or experiment with alternative formulations of generic medicines are imported from major suppliers abroad. Generally, drug discovery and development efforts are completely lacking.

There are more than 20 pharmaceutical firms in Ethiopia, with three fully locally owned, one foreign and 18 joint ventures. Of these, nine produce generic human medicines and the others engage in veterinary drugs, medical supplies, medical equipments and packaging such as empty hard gelatin capsules. From the nine producing generic human medicines, only two are GMP certified [31,32].

The local production of raw materials is extremely limited, thus almost all raw materials must be imported. Active pharmaceutical ingredients and excipients, as well as most packaging materials are imported. Reportedly, the only raw materials produced locally are sugar for syrups. The government of Ethiopia has been constructed Kilinto industrial park so as to provide physical and regulatory infrastructure for pharmaceutical firms. However, active and inactive pharmaceutical ingredients should still be imported [32].

Food, beverage and Pharmaceutical Industry Development Institute (FBPIDI) was established in 2014 under ministry of trade and industry (MOTI) to support the development of the food, beverages and industries. Its mandate is to support firms operating in the two industries through R&D, training, technology transfer, consultancy and facilitating access to export markets. FBPIDI is heavily dominated but its food and beverages activities, which account for approximately 75-80 percent of all activities. Of its 24 directorates, 20 are on food and beverages, and four on pharmaceuticals. It is underfunded and understaffed, has no pharmaceutical research laboratories with the requisite equipment, faces large skill gaps. Unless its pharmaceutical arm is restructured, it cannot meet the minimum mandate in current form [34].

- ***Community pharmacy:*** Also known as a retail pharmacy, the community pharmacy is the most well known type of pharmacy. It is this type that is most traditionally known as the pharmacist or chemist shop.

This is second important sector that absorbs pharmacist work forces in Ethiopia. A community pharmacist usually works in a store that provides the community with access to the medications they need, as well as advice to promote the safe and effective use of the medicines they provide. Community pharmacists are the most accessible professionals across the globe. Helping patients with the reimbursement of drug expenses, supervising pharmacy technicians and keeping inventory of the drugs stocked also make up part of their duties. Reimbursement is never implemented in Ethiopia. There are three categories of community retail outlets in Ethiopia, namely pharmacy, drug shop and drug vendor. Pharmacy demands a licensed pharmacist. There are over 1000 pharmacies, over 4000 drug shops and about 600 drug vendors in Ethiopia [26].

- ***Hospital pharmacy:*** The Hospital Pharmacy Services is important in ensuring that medicines are available and used safely and effectively by informed patients and professionals, both within the hospital and by ambulatory patients. Specifically, hospital pharmacy services include prescription validation and processing, formulary management, adverse drug reactions reporting, identification of potential drug-drug interaction and complementing drugs and therapeutics committee. Besides, small scale IV fluids, oxygen and compounding of extemporaneous preparations are also one of the most important services of hospital pharmacy sector. More emphasis is now given on Clinical Pharmacy practice in all hospitals and drug information services to ensure that patients get most of the benefits of modern medicines and they are not exposed to the risk or adverse effects. In Ethiopia, hospital pharmacy services embrace majority of pharmacy workforces [25,36,37].

- ***Drug information :*** Pharmacists also work in drug information centers (DIC). The provision of drug information (DI) is among the fundamental professional responsibilities of all pharmacists. Recent practice trends, including increased provision of medication therapy management (MTM) services and efforts to obtain provider status, have placed pharmacists in increasingly complex patient-care roles and necessitated a higher level of competence by all pharmacists in meeting DI needs. Drug information may be patient specific, academic (for educational purposes), or population based (to aid in the decision-making process for evaluating medication use for groups of patients). The goal of providing carefully evaluated, evidence-based recommendations to support specific medication-use practices is to enhance the quality of patient care, improve patient outcomes, and ensure the prudent use of resources. Pharmacists providing DI should use professional judgment and trusted drug information resources to meet health care organizations' and patients' needs and circumstances. In Ethiopia, The School of Pharmacy/Addis Ababa University (SOP/AAU) has established a model DIC at Tikur Anbessa Specialized Hospital in 2009. Since then efforts have been made by various institutions to initiate the provision of DIS at public health facilities including St. Paul's Hospital Millennium Medical College which was officially started provision of DIS in March 2010. The initiation of clinical pharmacy service and

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issuance of national DIS SOP are also important milestones towards the provision of DIS. Following these initiatives, hospitals and teaching institutions have started providing DIS. Several other drug information services established shortly thereafter leading more than 126 DIS in Ethiopia by a concerted effort of EPSA in collaboration with USAID/SIAPS. In addition, private institutions have also initiated provision of DIS. These include Tossa Pharmacy DIC at Dessie and Gishen Pharmacy DIC in Addis Ababa [38].

- ***Nuclear pharmacy/radiopharmacy:*** Nuclear pharmacy is a specialty area of pharmacy practice involved with the preparation of radioactive materials to improve and promote health through the safe and effective use of radioactive drugs to diagnose and treat specific disease states. Radiopharmaceuticals have become the most important and sensitive tools in the detection, diagnosis and targeted therapy of diseases. The preparation of radiopharmaceuticals for human use requires that it is carried out in well defined and controlled conditions to avoid the risk contamination with microbes, pyrogens and particulate matter as well as cross contamination with other radiopharmaceuticals. Most radiopharmaceuticals are parenterally administered and must therefore be prepared in such condition, and using such techniques and procedure, that guarantee sterility of the product. Every procedure undertaken should be done according to the clearly defined protocol and under the right conditions so as to build quality into the product. There is radiopharmaceuticals preparation unit at oncology department at College of Health Sciences, Addis Ababa University [29].

- ***Clinical pharmacy:*** These specialty pharmacy services do exist in countries (e.g. USA, Canada etc.) where clinical pharmacy services are fully incorporated in healthcare service delivery systems. The inception of clinical pharmacy in Ethiopia is Jimma University. Although clinical pharmacy education has started both in undergraduate and postgraduate programs, the service is almost non-existent in Ethiopia due to many reasons. First, the curriculum itself must be revisited. Second, the healthcare system in Ethiopia does not still allow clinical pharmacy services. Third, the project known as Auditable Pharmaceutical Transactions and Services (APTS) has by itself significantly impeded clinical pharmacy services. APTS is not a problem by itself, but the implementation procedure undermined the clinical pharmacy services in the wards. As a result, the clinical pharmacists were forcefully taken back to counters. Moreover, APTS was interpreted as holistic pharmacy services that include clinical pharmacy services, which is deadly oversight. Fourthly, other health professionals have also misunderstood the roles of clinical pharmacists. They consider clinical pharmacists as professionals breaching professional boundaries and trying to take the roles of physicians, nurse and others. This notion is time and again wrong. Clinical pharmacists, like industrial pharmacists, community pharmacists and regulatory pharmacists, are pharmacists; they are not new categories of professionals. Clinical pharmacists deal with drugs as any other pharmacists. But, they focus on pharmacotherapeutic management of diseases. These all have impeded the already struggling clinical pharmacy services in Ethiopia. Contrary to these misunderstandings, involving clinical pharmacists in the healthcare team leads to clinically relevant and well accepted optimization of medicine use in a resource limited settings [3,39-41].

- ***Veterinary pharmacy:*** Although University of Gondar has launched Bachelor of veterinary pharmacy program, the graduates could not be mandated to run veterinary drugs and veterinary pharmacy services. The veterinary pharmacy service is rather integrated in veterinary medical practice and run by veterinarians. Besides, a veterinary pharmacy service is owned by Federal Ministry of Agriculture, not Federal Ministry of Health. The regulation of veterinary drugs is also weak in Ethiopia [42-45].

Drug

Introduction

The word drug comes from a French word 'Drogue' meaning a dry herb. It can be defined as: "any substance other than food products that are used or intended to be used to modify or explore physiological processes or pathological states, for the benefit of the recipient." A given drug can enhance the biological activity (e.g. increase in heart rate), inhibit biological activity (e.g. decrease in blood pressure), stabilize biological activity (e.g. stabilizing neuronal discharge), kill microorganisms (e.g. penicillins) or prevent pregnancy (e.g. norgestrel). The two most important properties of a given drug are safety and efficacy.

The terminologies drug, pharmaceutical, medicine and medication are used interchangeably in the context of today's pharmacy practice. The same notion applies to this book as well. However, there are minor differences among them. A pharmaceutical is a standard drug recognized in an official pharmacopeia or formulary. "Medicine" and "medication" are two words that are usually used interchangeably. The word "medicine" does mean a substance used in the diagnosis, treatment, cure, mitigation and prevention of diseases on one context; and the art of diagnosis, treatment, and prevention of diseases that can affect both the body and the mind, in different context. Medication, on the other

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hand, is defined as the process (e.g. self medication) of treating an illness with medicine. A pharmaceutical, medicine and medication only refer to legal or medically used substances, but the term drug includes all forms of substances; legal or illegal, medically used or not [42-45].

Drugs are derived from a wide variety of different sources, including plants, minerals, animals, synthetic and DNA sources [46].

- Plants e.g. Quinidine from cinchona bark, digoxin from foxglove plant and morphine from opium poppy plant.
- Minerals e.g. Milk of magnesia (Mg) , Zinc oxide (Zn)
- Animals: e.g. Insulin from pancreas of the cow or pig
- Synthetic: Acetylsalicylic acid (Aspirin) Meperidine, Diphenoxylate, Co-Trimoxazole.
- Recombinant DNA: Hepatitis B vaccine, insulin and the growth hormone.

Drug discovery and development process

Drug discovery and development is the process of bringing a novel drug from "bench to bedside". The process is a complex and expensive (multimillion dollar) endeavor undertaken by pharmaceutical companies, academic scientists, and governments.

It can take 10 to 15 years for a drug to be designed, developed and approved for use in patients. Before a drug can reach a patient, it must go through rigorous testing to determine whether it is safe, effective at treating the condition it was developed for, and to ascertain the correct dosage and appropriate administration route. Many scientists including biologists, chemists, biochemists, microbiologists, pharmaceutical scientists, clinicians and pharmacists take part throughout the processes [47,48].

There are five steps in drug discovery and development processes.

Discovery and Development

Drug discovery is the process by which new drugs are discovered. Historically, drugs were discovered through identifying the active ingredient from traditional remedies or by serendipitous (by chance) discovery. Later chemical libraries of synthetic small molecules, natural products or extracts were screened in intact cells or whole organisms to identify substances that have a desirable therapeutic effect in a process known as classical pharmacology. Since sequencing of the human genome which allowed rapid cloning and synthesis of large quantities of purified proteins, it has become common practice to use high throughput screening of large compounds libraries against isolated biological targets which are hypothesized to be disease-modifying in a process known as reverse pharmacology [48,49].

Before a drug can even begin to be tested, it must first be researched. This will often start not with the drug itself, but with the identification of a possible target for a drug to act upon. This target could be a protein or pathway in the body which has been implicated in a particular disease or condition. Diseases and conditions that we know more about are easier to determine targets for. Once a target has been identified, Once a target is identified it is validated to verify its suitability for pharmaceutical development. Target validation can involve a range of techniques, such as developing 'knockout' animals which lack certain genes, and seeing if the disease proceeds in the same manner in these animals. Once a target has been identified and validated, the search to for the "hit" begins. A "hit" is a compound that interacts with the target of interest. Numerous screening approaches can be used to identify a "hit" compound. This will involve the laboratory testing of a huge number of compounds, often 10,000 or more, to determine which show some activity against the target. At this stage, it's unlikely that the perfect candidate will be obtained, but compounds that show promise will be identified. These compounds can then be tweaked by the science of medicinal chemistry in attempt to improve potency against the target. This is known as 'lead optimization'. In the hit to lead process, hits are evaluated and optimized in limited way into lead compounds. These compounds then move on to the lead optimization process i.e. the lead compounds are Synthesized and modified to improve potency and reduce side effects. The drug discovery process ends when one lead compound (also called new chemical entity-NCE) is found for a drug candidate, and the process of drug development starts [45,48].

Drug development is the process of bringing converting NCE into a viable drug. The development of drugs in the pharmaceutical industry is a long-term process, often taking more than a decade from the start of a research project to the appearance of a drug on the market. That process involves several decision points, such as the choice of the candidate drug after the preclinical screening phase, the investigational new drug (IND) application before testing the compound for the first time in man, and finally the new drug application (NDA) which summarizes the data obtained

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from all the studies needed for marketing approval of the drug as a medicine. Regulatory approval is required prior to the IND and before marketing is licensed (NDA). Substance quality and its specifications are based on substance analysis, and that knowledge is later used for quality control during full-scale production. Product analysis involves dealing with the various formulations and starts after the IND has been approved. The results from such work lead to specifications that form the basis for the quality control of the product. For both substances and formulations there is an increasing interest in the introduction of process pharmaceutical analytical chemistry.

It includes pre-clinical research (microorganisms/animals) and clinical trials (on humans) and may include the step of obtaining regulatory approval to market the drug. The process of drug discovery and development is regulated at the national level. For example in USA,US Food and Drug Administration, simply FDA and in Ethiopia by Ethiopian Food and Drug Administration and Control Authority (EFDA, previously known as FMHACA, DACA) [45,48].

Preclinical studies

The goal of preclinical studies is to deliver one or more clinical candidate molecules, each of which has sufficient evidence of biologic activity at a target relevant to a disease as well as sufficient safety and drug like properties so that it can be entered into human testing. Most discovery programs seek to produce more than one candidate molecule because, many molecules do not move through the entire process because of problems with safety, kinetics, potency, intellectual property protection, or other factors.

Before testing a drug in people, researchers must find out whether it has the potential to cause serious harm, also called toxicity. These can involve both *in vitro* and *in vivo* experiments. *In vitro* is latin for 'within glass' and involves tests on cells or molecules outside of their usual biological surroundings. This can be useful in determining the degree of the drug's efficacy, and can also give information on its toxicity, though it doesn't give information on all the ways in which it might affect organisms; that's where *in vivo* testing comes in. *In vivo* is latin for 'in the living'. *In vivo* testing involves the use of animals to test drugs.

Although efforts are being made to reduce the amount of animal testing, it is still used because it can give information about the effects of drugs that *in vitro* testing cannot. *In vivo* testing can tell us how the drug behaves in the body of an organism; it might have some unpredictable effects, so this is important to know. Of course, animals aren't the perfect models for humans either. Generally, mammals that provide relatively good models are used, such as rodents. However, regulatory bodies usually require tests to have been carried out on at least two different mammalian species, including one non-rodent species, before the drug can be permitted to start human clinical trials. The hope is that these animal tests can detect any serious side effects before humans are exposed to the drug [45].

Clinical trials

While preclinical research answers basic questions about a drug's safety, it is not a substitute for studies of ways the drug will interact with the human body. "Clinical research" refers to studies, or trials, that are done in people. To avoid bias, clinical trials should be placebo-controlled, randomized and double-blind. In a properly randomized trial, neither the patient nor the investigator should have any influence on which treatment the patient will end up receiving. The double-blind technique, whereby neither subject nor investigator is aware at the time of the assessment which treatment is being used, is intended to minimize subjective bias. While many clinical trials include a placebo group that shows improvement, few have compared this group directly with untreated controls, particularly where the natural history of the disease is symptom resolution without any intervention. There are also growing numbers of pragmatic trials where the new treatment is compared against 'standard or usual' care, rather than the rather artificial construct of a placebo dummy pill that does not represent what the patient would actually receive in clinical practice [48,50].

Moreover, both type I errors (concluding that the new drug is better when that happens actually due to chance) and type II errors (concluding that the new drug is not different from the existing ones because a real difference has escaped detection) should be minimized. This is true when the methodological quality, sample size and number of end-point events are increased.

Clinical outcome measures may comprise:

- Physiological measures (e.g. blood pressure, liver function tests, airways function);
- Subjective assessments (e.g. pain relief, mood);
- Long-term outcome (e.g. survival or freedom from recurrence);
- Overall 'quality of life' measures;

Drugs must receive a clinical trial authorization (CTA) in the EU, or submitted to the FDA as an investigational new

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drug (IND) in the US, before they can begin clinical trials. Generally speaking, all experiments on human subjects require approval by an independent ethics committee.

Clinical trials are divided into three categories: phase 1, phase 2, and phase 3 [42-45,48].

Phase 1 trials

Phase 1 trials are the first tests of the drug involving human participants, and commonly involve 20-100 subjects. The primary purpose is to establish safety. The study design is open label randomized one. Phase 1 studies are closely monitored and gather information about how a drug interacts with the human body. Researchers adjust dosing schemes based on animal data to find out how much of a drug the body can tolerate (safe dose) and what its acute side effects are. As a Phase 1 trial continues, researchers answer research questions related to how it works in the body, the side effects associated with increased dosage, and early information about how effective it is to determine how best to administer the drug to limit risks and maximize possible benefits. This is important to the design of Phase 2 studies. Phase 1 trials might require several months to accomplish.

Approximately 70% of drugs move to the next phase.

Phase 2 trials

Phase 2 trials involve a larger number of subjects, usually 50-500. The main purpose is to ensure preliminary efficacy and collect information on therapeutic doses and safety. The design is randomized, double-blind and placebo-controlled. A placebo is a dummy medicine containing no active ingredient, which the patient believes is the real thing. The 'placebo response' is widely believed to be a powerful therapeutic effect, producing a significant beneficial effect in about one-third of patients.

Controlled trials that compare the drug to a placebo will be conducted in order to determine how effective it is in humans. These studies aren't large enough to show whether the drug will be beneficial. Instead, Phase 2 studies provide additional safety data that is used to refine research questions, develop research methods, and design new Phase 3 research protocols. Phase 2 trials can take several months to 2 years. Approximately 33% of drugs move to the next phase.

Phase 3 trials

Study Participants: Sometimes known as pivotal studies, these studies involve 300 to 3,000 participants who have the disease or Condition. The design is randomized, double-blind and placebo-controlled. The main purpose is to confirm efficacy and safety. Phase 3 studies are designed to demonstrate whether or not a product offers a treatment benefit to a specific population. Phase 3 studies provide most of the safety data. In previous studies, it is possible that less common side effects might have gone undetected. Because these studies are larger and longer in duration, the results are more likely to show long-term or rare side effects. Phase trials can take 1 to 4 years.

Review & approval

If sufficient evidence is obtained from early tests, preclinical and clinical research that a drug is safe and effective for its intended use, a New Drug Application (NDA) can be filed for market approval. Approval involves the regulatory body examining the evidence and considering whether the drug's benefits outweigh its risks. No drug is absolutely safe, and what the regulatory body decrees to be an acceptable risk will often depend on what the drug is designed to treat. Some drugs are given priority in the approval process over others. Drugs which provide a treatment which did not previously exist (e.g. drug for COVID-19) will be fast-tracked over drugs which are similar to drugs that already exist on the market. If the regulatory body is satisfied that the benefits of the drug are significant enough to make the risks worthwhile, it will meet with approval, a process that usually takes around a year. Once approved, prescribing information will be designed and refined. This is referred to as "labeling." Labeling accurately and objectively describes the basis for approval and how best to use the drug [48,50].

After approval for marketing, the authorities exercise control of products on the market and require post production stability data. Public interest in the quality of drugs is also reflected in the compilation of substance monographs in compendia that are known as pharmacopoeias. In addition to collections of substance monographs these pharmacopoeias contain general analytical methods and some also contain monographic requirements on the formulation of the substances.

Governments worldwide have created provisions for granting access to drugs prior to approval for patients who have exhausted all alternative treatment options and do not match clinical trial entry criteria. Often grouped under the

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labels of compassionate use, expanded access, or named patient supply, these programs are governed by rules which vary by country defining access criteria, data collection, promotion, and control of drug distribution.

Post-marketing safety surveillance (phase 4 clinical trial)

The drug reaching the market is not the end of the road in drug discovery and development process. Even though clinical trials provide important information on a drug's efficacy and safety, it is impossible to have complete information about the safety of a drug at the time of approval. Despite the rigorous steps in the process of drug development, limitations exist. Therefore, the true picture of a product's safety actually evolves over the months and even years that make up a product's lifetime in the marketplace. Thus, the safety and effectiveness of the drug must be monitored in several thousand patients/ general population, even after approved for market. Post-marketing Safety Surveillance is the term used for the monitoring of a drug after it has received approval and has reached the market. It is designed to evaluate the long-term safety and efficacy of a drug, potential "real-world" problems with formulation, exploring the use of the drug for additional indications, unapproved indications (off-label use), and additional age groups or to develop an alternative route of administration. The design is open label and the duration is unlimited. There is still a possibility that rare side effects might come to light that were not observed in previous clinical trials. Probably the most famous example of a drug that reached manufacture and distribution but was later found to have serious side effects is that of thalidomide [48,50,51].

Comparative Effectiveness Research (CER)

An understanding of the distinction between efficacy and effectiveness research is not only crucial when conducting research but also interpreting results from studies and deciding how applicable it may be to clinical practice and patients who may have less access and less adherence to medications. Given a growing focus on evidence-based medicine and pay-for-performance measures, providers must base clinical decisions on the best available evidence. Although some prioritize efficacy data from Randomized Controlled Trial (RCT), others view effectiveness data as more pertinent to real-world clinical practice decisions.

Efficacy studies investigate the benefits and harms of an intervention under highly controlled conditions. A placebo controlled RCT design is ideal for efficacy evaluation because it minimizes bias through multiple mechanisms, such as standardization of the intervention and double blinding. Although this has multiple methodologic advantages and creates high internal validity, it requires substantial deviations from clinical practice, including restrictions on the patient sample, control of the provider skill set and limitations on provider actions, and elimination of multimodal treatments. Effectiveness studies (also known as pragmatic studies) on the other hand, examine interventions under circumstances that more closely approach real-world practice, with more heterogeneous patient populations, less-standardized treatment protocols, and delivery in routine clinical settings. Effectiveness studies may also use a RCT design; however, the intervention is more often compared with usual care, rather than placebo. Minimal restrictions are placed on the provider actions in modifying dose, the dosing regimen, or co-therapy, allowing tailored therapy for each subject. Although effectiveness studies sacrifice some internal validity, they have higher external validity than efficacy studies [50].

Clinicians have historically been frustrated by the lack of consideration of external validity in RCTs, other efficacy studies, and guidelines. Accordingly, there has been a call for studies whose results can be more readily applied to everyday clinical practice i.e. comparative effectiveness research (CER). CER is defined as ''the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition, or to improve the delivery of care.'' The purpose of CER is to assist patients, providers, and policy-makers in making informed decisions that can improve health care both at the individual and population levels. As suggested by the name, CER places an emphasis on effectiveness studies, conducted in settings similar to real world clinical practice, to maximize external validity of any results.

Drug Development and Pharmacogenomics

Genes, which are made up of DNA, are a set of instructions that act like blueprints and tell our bodies how to grow and work. We have two copies of each gene in every cell of the body, one from our mother and one from our father. The *gene* for a specific enzyme is a set of instructions for making that enzyme. Small changes in this gene can change how well the enzyme works to break down medications. Knowing the gene status of a specific enzyme will help choose the best doses of medications for a patient. Some people have enzyme that is inactive enzyme or reduced activity, while others have normal or increased enzyme activity. Most drug discoveries are based mainly on the majority of population (about 60%), who have normal enzyme activity. Thus, the dosage ignores about 40% of population (inactive, reduced or increased enzyme activity) [52-60].

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There are four categories of populations based on the status of a specific enzyme (:e.g. CYP1A2, CYP2B6, CYP2D6, CYP2C9, CYP2C19, CYP3A4 etc). One can have inactive CYP2D6 enzyme, but active CYP2C9 enzyme. Thus, it is specific to each enzyme.

a. Poor Metabolizers (PMs): those who have inactive enzyme. They have poor enzyme activity and thus cannot metabolize a given drug that must be metabolized by specific enzyme. For example, those who have inactive CYP2D6 enzyme fail to metabolize substrates of CYP2D6 enzyme. However, they may have still active CYP2C9, CYP2C19 or CYP3A4. PM cannot metabolize a given drug and thus require a change into alternative drug. If they receive the same drug as others, they are most likely to experience unwanted side effects or toxicity. Moreover, if the drug is a prodrug, it cannot be converted into active drug.

b. Intermediate Metabolizers (IMs): Those who have below normal/reduced enzyme activity. IMs are also called *slow metabolizers*. IMs require lower doses than the usual standard dosages. If IMs receive standard dosages, they are more likely to experience unwanted side effects or toxicity. Moreover, if the drug is a prodrug, only little would be converted into active drug.

c. Extensive Metabolizers (EMs): Those who the normal enzyme activity. EMs are also called *fast metabolizers* or *rapid metabolizers*. Ems should respond to standard dosages of a drug. Most people are EMs. EMs are categories of population in which most dosing regimens have been worked out in clinical trials. There is no need for dosage adjustments unless other factors (e.g. renal function, hepatic function, drug-drug interactions etc.) are considered.

d. Ultrarapid metabolizers (UMs): those who have highly increased enzyme activity. EMs are also known as ultra-fast metabolizers. EMs will require a higher dose than the standard dosages they eliminate the drug more quickly. If they take the usual standard dosages, treatment failure might occur.

In addition to CYP enzymes, other enzymes, receptors and transporter proteins might be affected by genetic differences. Thus, pharmacogenomic differences should be taken into account in designing dosage regimens.

Some drugs, such as codeine, will not be effective in people without the requisite enzymes to activate them.

Drug products and naming

New drugs are patent protected when they are approved for marketing. This means that only the sponsor has the right to market the drug exclusively. Once the patent expires, other drug manufacturers can develop the drug, which will be known as a generic version of the drug. Generic drugs are comparable to brand name drugs and must have the same: Dosage form, Strength, Safety, Quality, Performance characteristics and intended use. Because generic drugs are comparable to drugs already on the market, generic drug manufacturers do not have to conduct clinical trials to demonstrate that their product is safe and effective. Instead, they conduct bio-equivalence studies and file an Abbreviated New Drug Application [61,62].

Most drugs have three names; brand name, generic name and chemical name [42-45].

1. **Chemical name:** It is derived using rules established by the International Union of Pure and Applied Chemistry (IUPAC). These rules allow scientists all over the world to name structures the same way so that any other scientist will know what structure is being referred to based on the name. Since *chemical* names are usually long and complicated, the drugs are given a standard, shorter *generic* name.

E.g. 7-chloro-1,3-dihydro-1- methyl-5-phenyl-2H-1,4-benzodiazepin-2-one for Diazepam; N-acetyl-para-aminophenol for Acetaminophen.

2. **Brand names (Proprietary name):** It is chosen by the company that makes it. The name is often chosen to be memorable for advertising, or to be easier to say or spell than generic name. The brand name is usually written most clearly (often in large print) on any packaging. However, you will always see the generic name written somewhere on the packet (often in small print). The original manufacturer of a drug receives a patent on the drug and is the only manufacturer who can produce and sell the drug during this patent period (8-20 years). The goal of patent right is to honor the innovator and also to compensate the cost spent during the discovery process. Drug produced by this original manufacturer is called brand product. It continues to be "brand product" even after the patent period expires. The patent period is restricted just to provide other manufacturers to produce the less expensive generic products for the sake of people.

E.g Valium for Diazepam, Bactrim for co-trimoxazole, Losec for Omeprazole

3. **Generic name (Non-proprietary):** Generic name is an official, a scientific or an international name given to a given drug. It is non-propriety (unclaimed)given by a regulatory body (e.g. FDA). Currently, there is only one generic name

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for a given product across the globe. Previously, more than one generic name was given to few drugs (Acetaminophen vs. Paracetamol, Salbutamol vs. Terbutaline, Glyburide vs Glibenclamide) by USA and Canada regulatory bodies. There is no drug that has no generic name. Even the brand product has both generic name as well as brand name. But, the manufacturer prefers to advertise its brand product with its own (proprietary) brand name.

When patent protection/period for the brand product expires, a bioequivalent version may be produced by interested manufacturers and sold as a "generic" version/product, typically at a significant discount below the brand product. Generic products are cheaper because these manufacturers have not had the same expenses as the original manufacturer of the brand product. Generic products have similar dosage forms, route of administration, comparable risks, safety, and strength as the generic product. However, they might have different colors, flavors, or combinations of inactive ingredients than the brand product.

Interested manufacturers can use the official generic name for their generic products or use their own trade names. But, they cannot use the brand name by the original manufacturer [61,62].

Bioequivalence testing

An Abbreviated New Drug Application (ANDA) is an application for a generic drug approval for an existing licensed medication or approved drug. The ANDA is submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs, which provides for the review and ultimate approval of a generic drug product. In other countries, it is submitted to respective regulatory bodies. There is a bioequivalence center in Ethiopia as well. It is situated at school of Pharmacy, College of health Sciences, Addis Ababa University. Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, low cost alternative to the public.

A generic drug product is one that is comparable to a patented drug product in dosage form, strength, route of administration, quality, performance characteristics and intended use. All approved products, both innovator and generic, are listed in FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book).

Generic drug applications are termed "abbreviated" because (in comparison with a New Drug Application) they are generally not required to include preclinical (animal and in vitro) and clinical (human) trial data to establish safety and effectiveness. Instead, generic applicants must scientifically demonstrate that their product is bioequivalent (i.e., performs in the same manner as the innovator drug). One way scientists demonstrate bioequivalence is to measure the time it takes the generic drug to reach the bloodstream in 24 to 36 healthy volunteers. This gives them the rate of absorption, or bioavailability, of the generic drug, which they can then compare to that of the innovator drug. The generic version must deliver the same amount of active ingredients into a patient's bloodstream in the same amount of time as the innovator drug. In cases of topically active drugs, the bioequivalence of a drug can be demonstrated by comparing drugs dissolution or transdermal drug absorption is compared with the innovator drug. In cases of systemically active drugs, active drug blood concentration of that drug is compared with the innovator drug [61,62-65].

Good manufacturing practices

Any company can make mistakes, but adherence to good manufacturing practices (GMP) makes mistakes less likely and easier to correct. GMP requires drug producers to follow a cleaning protocol laid out in their standard operating procedures and to follow cleaning with validation testing. Regulators prefer to use "cGMP" to say current Good Manufacturing Practices, to emphasize that the expectations are dynamic. cGMP is designed to minimize the risks involved in any pharmaceutical production that cannot be eliminated through testing the final product [66].

Manufacturers, processors, and packagers of drugs, medical devices and blood should take protective steps to ensure that their products are safe, pure, and effective. More specifically, companies should adhere to GMP norms to minimize or eliminate instances of contamination, mix-ups, and errors' so as to protect the consumers from purchasing a product, which is not effective or even dangerous. Generally, GMP regulations address issues including record keeping, personnel qualifications, sanitation, cleanliness, equipment verification, process validation, and complaint handling [67].

A factory run in accordance with best practices does not need to be the most technologically advanced or use state-of-the-art equipment. However, good quality comes at a price, i.e. there are costs to bring a factory up to standard, train staff on appropriate protocols, and observe them consistently [66,67].

Pharmaceutical fraud

Drugs safety and efficacy are the most important criteria in ensuring optimal treatment from medicines and are currently receiving increased attention in an era of globalization and generic manufacturing. Thus, not only good manufacturing practice, but a reliable drug supply is fundamental to public health. A country with weak regulatory

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system is a likely victim of pharmaceutical fraud, which is related to poor quality drugs. Poor quality drugs fail to meet the specifications set by the regulatory authority and delineated in a pharmacopeia or the manufacturer's dossier. These include drugs with less(substandard) or none(counterfeit) of the stated active ingredients, with added, sometimes hazardous, adulterants, substituted ingredients, completely misrepresented, or sold with a false brand name. Poor quality drugs will find the easiest access when a vacuum occurs in the market. This vacuum often occurs when there is low supply of essential drugs or when the available drugs are not affordable. Pharmaceutical fraud can happen either accidentally or deliberately [68].

Poor quality drugs are associated with fatal health (drug resistance, therapeutic failure, toxicity, death etc.) and economic consequences. Moreover, they are linked with organized crime. Furthermore, it diminishes trust between patients and healthcare providers. Thus, poor quality drugs should be identified through all possible means, i.e. chemical analysis, physical analysis, authentication of source, and package inspection etc. However, since quality-control assays generally test for the presence of the known ingredients, not the wide range of possible unknown contaminants, it will not be an easy task [69].

Generally, strict adherence to GMP, reliable drug supply chain management system and strong regulatory system are critical in countering pharmaceutical fraud.

The Science of drug formulations

Dosage forms (formulations) are pharmaceutical drug products in the form in which they are marketed for use, with a specific mixture of active ingredients (the therapeutic drug itself) and inactive components (excipients), in a particular configuration, and apportioned into a particular dose. Suitable dosage forms are needed for protection of the drug from destructive influences of the atmospheric oxygen or moisture, for protection of drug from destruction from gastric acid on oral administration, to mask bitter taste and foul odor (palatability), to provide extended drug action through controlled release mechanism etc. Early drug preparations from plants, animals, and minerals were so distasteful. The search for improved product formulations founded the disciplines of *pharmaceutics, the science of formulation.* During formulation development, the excipients are chosen carefully so that the active ingredient can reach the target site in the body at the desired rate and extent. An excipient is a substance formulated alongside the active ingredient of a drug included for the purpose of long-term stabilization, bulking up solid formulations that contain potent active ingredients in small amounts, or to confer a therapeutic enhancement on the active ingredient in the final dosage form, such as facilitating drug absorption, reducing viscosity, or enhancing solubility. The selection of appropriate excipients also depends upon the route of administration and the dosage form, as well as the active ingredient and other factors. Notable examples are antiadherents(e.g. magnesium stearate),binders (e.g. starch, polyvinylpyrrolidone (PVP), polyethylene glycol (PEG)), colors (e.g. azo dyes), disintegrants (e.g. crosslinked sodium carboxymethyl cellulose),flavors can be used to mask unpleasant tasting active ingredients and improve the acceptance that the patient (e.g mint, , raspberry vanilla), glidants(e.g silica gel,talc), lubricants(stearin), preservatives(citric acidsodium citrate, parabens), sweetners, solubilizers,buffers, tonicity modifiers, viscosity enhancers/reducers, surfactants, chelating agents etc [70].

Formulations are affected by factors such as particle size, polymorphism, pH, and solubility, as all of these can influence bioavailability and hence the activity of a drug. It is unlikely that formulations are finalized by the time clinical trials commence. This means that simple preparations are developed initially for use in phase I clinical trials. These typically consist of hand-filled capsules containing a small amount of the drug and a diluent. Proof of the long-term stability of these formulations is not required, as they will be used (tested) in a matter of days. By the time phase III clinical trials are reached, the formulation of the drug should have been developed to be close to the preparation that will ultimately be used in the market. Knowledge of stability is essential by this stage, and conditions must have been developed to ensure that the drug is stable in the preparation. Stability studies are carried out to test whether temperature, humidity, oxidation, or photolysis (ultraviolet light or visible light) have any effect, and the preparation is analyzed to see if any degradation products have been formed.

Notably, the route of administration for drug delivery is dependent on the dosage form of the substance in question. Various dosage forms may exist for a single particular drug, since different medical conditions can warrant different routes of administration. Additionally, some drugs are not suitable for common routes of administration. As an example, drugs like insulin, heparin, enfuvuritide cannot be given orally because of extensive metabolism in the gastrointestinal tract (GIT) before reaching the blood stream, and thereby incapable of sufficiently reaching its therapeutic target destinations [60,71].

Formulated drugs are stored in container closure systems for extended periods of time. These include blisters, bottles, vials, ampoules, syringes, and cartridges. The containers can be made from a variety of materials including glass, plastic, and metal. The drug may be stored as a solid, liquid, or gas. It's important to check whether there are

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any undesired interactions between the preparation and the container. Pharmaceutical packaging (or drug packaging) is the packages and the packaging processes for pharmaceutical preparations. It involves all of the operations from production through drug distribution channels to the end consumer. Pharmaceutical packaging is highly regulated but with some variation in the details, depending on the country of origin or the region. Several common factors can include: assurance of patient safety, assurance of the efficacy of the drug through the intended shelf life, uniformity of the drug through different production lots, thorough documentation of all materials and processes, control of possible migration of packaging components into the drug, control of degradation of the drug by oxygen, moisture, heat, etc., prevention of microbial contamination, sterility, etc. Packaging is often involved in dispensing, dosing, and use of the pharmaceutical product. Communication of proper use and cautionary labels are also regulated. Packaging is an integral part of pharmaceutical product. Bulk pharmaceuticals can be shipped to another pharmaceutical company for further processing, to a contract packager for forming unit packs, to international customers, etc [70-74].

Common dosage forms

Dosage forms come in many types, depending on the method or route of administration. Solid dosage forms, semi-solid dosage forms, liquid dosage forms, and gaseous dosage forms are used for the diagnosis or treatment of the disease by various routes. Solid dosage forms are the most significant and most commonly used dosage forms in pharmaceuticals; it has one or more unit dose of medicament. The tablet is the most commonly used oral solid dosage forms. Solid dosage forms have high precision, lowest variability, better stability and accurate dosing [70-74].

Solid dosage forms

The common used solid dosage forms are tablet/caplet/pellets/pills, capsules/spansules, powder, granules, and lozenges/pastilles/troches.

Tablet: Tablets are solid unit dosage forms containing granulated or powdered drugs that are compressed or molded into round or other shapes. They usually contain a diluent, a binder, a disintegrator and a lubricant. A caplet is a smooth, coated, oval-shaped medicinal tablet in the general shape of a capsule. Many caplets have an indentation running down the middle so they may be split in half more easily. Caplets are easier to swallow. Pellets are small sterile spheres of tablets.

Tablets are usually taken orally, but can be administered sublingually, buccally, rectally or vaginally. Tablets can be swallowed, chewed, put under tongue, attached to the gum or inserted. It can be coated (enteric coated, film coated) or prepared as immediate release or delayed release forms.

Film/sugar coatings are necessary for tablets that have an unpleasant taste. If the active ingredient of a tablet is sensitive to acid, or is irritant to the stomach lining, an enteric coating can be used, which is resistant to stomach acid, and dissolves in the less acidic area of the intestines.

Traditional drug delivery system has been characterized by immediate release and repeated dosing of the drug which might lead to the risk of dose fluctuation, this arises the need of a formulation with control release that maintain a near-constant or uniform blood level. Such formulations are called delayed-release/depot preparations. Delayed-release formulations are drug delivery systems that are designed to achieve prolong therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose.

The desire to maintain a near-constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use.

Delayed-release dosage forms are dosage forms designed to release (liberate) a drug at a predetermined rate in order to maintain a constant drug concentration for a specific period of time with minimum side effects. This can be achieved through a variety of formulations, including liposomes and drug-polymer conjugates (an example being hydrogels). Delayed-release preparations can be either sustained release (SR) or Controlled Release (CR). SR maintains drug release over a sustained period but not at a constant rate, but CR maintains drug release over a sustained period at a nearly constant rate.

Quality control of tablets involves various tests which require keen attention. To ensure that established product quality standards are met, these tests must be performed during production (in-process controls) and verified after the production of each batch. The common tests include dissolution test, disintegrations test, hardness/crushing strength test and friability tests.

Tablets are often stamped with symbols, letters, and numbers, which enable them to be identified.

Capsule: A capsule is a gelatinous envelope enclosing the active drug in form of powder, granules, crushed tablets

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or liquids. They dissolve readily in the stomach and make the contents available for absorption. Capsules may be coated with substances that resist the action of gastric juice and do not disintegrate in the stomach but on reaching the intestines they dissolve in alkaline juices and release the drug. They can be designed to remain intact for some hours after ingestion in order to delay absorption. They may also contain a mixture of slow and fast release particles to produce rapid and sustained absorption in the same dose. Spansules are capsules that are filled with granules which dissolve at different rates, in effect causing sustained release.

Capsules are taken orally, but on occasions they may be administered rectally or vaginally.

The two main types of capsules are:

- **Hard gelatine capsule (Hardgels):** which contain dry, powdered ingredients or miniature pellets made by extrusion or spheronization. These are made in two halves: a smaller-diameter "body" that is filled and then sealed using a larger-diameter "cap".
- **Soft gelatin capsule (Softgels):** primarily used for oils and for active ingredients that are dissolved or suspended in oil.

Powder

A powder is a finely ground mixture of a drug and excipient. It should dissolve in water for oral use. Effervescent powders liberate carbon dioxide when dissolved in water making the preparation more palatable. Powder can also be prepared for parenteral use in ampoule. In this case, the powder must be reconstituted with water before injection.

Granule

Granules are larger than powders and are wetted, allowed to dry ground into course, irregular shaped pieces. Granules are more stable than powder.

Suppository/pessary

Suppositories are designed to be inserted rectally, vaginally or urethrally for local or systemic effects. The suppository base is an inactive ingredient, which melts or dissolves in the body cavity releasing the medication. Suppositories are especially ideal for pediatric and geriatric patients.

Lozenge/troche/pastille

Lozenges are drugs contained in a flavored sugar base to be dissolved slowly inside the mouth for local effects.

Semi-solid dosage forms

They are preparations designed for topical use. The most common semi-solid dosage forms are ointments, creams, lotions, gels, and pastes.

Ointments and Creams

Many medicines intended for skin application are packaged both as creams and ointments. The water and oil components of creams and ointments serve primarily as a "vehicle" to carry an active ingredient or medication.

An ointment is a preparation of a medication for topical use that contains an oil base. It is a preparation of water in oil. While ointments have a higher concentration of oil, creams have a higher concentration of water. Most ointments are 80% oil and 20% water. The oil component is made from hydrocarbons, such as mineral oil or petroleum jelly. Ointments feel greasy and are "occlusive", meaning they stay on the surface of the skin and are not well absorbed.

Ointments work better on dry skin conditions, such as psoriasis. They are occlusive, trapping moisture and absorbing much more slowly into the skin over time. They tend to stay on the skin much longer than creams for this reason. If you need to moisturize the skin, an ointment is a better choice. If you need a medication to penetrate deep into the skin, an ointment is a better choice as well, because they tend to stay on the skin much longer and creams will dry out before getting fully absorbed into the skin tissue. When is it best to use an ointment? Ointments are best used on dry skin. They are 'occlusive,' which means they trap moisture and are not well absorbed into the skin. Thus, they are able to keep the skin moist for longer periods of time. Being occlusive, an ointment will allow the medication to enter the skin more completely than a cream. The potency of a given corticosteroid for example may change depending on whether it is in cream or ointment form. At the same dosage, most topical corticosteroids will be classified as being stronger when packaged as an ointment as compared to a cream.

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A cream is a preparation of a medication for topical use that contains a water base. It is a preparation of oil in water. Creams are a mixture of roughly half water and half oil. They spread easily, are well absorbed, and wash off with water. In general, people prefer using creams to ointments since they are less sticky and heavy on the skin. Even though we think of creams as being moisturizing, given their higher water content and the evaporation that occurs following application, creams are better than ointments for treating oozing or "wet" skin conditions. Since the viscosity (thickness) of creams is less than that of ointments, they also work better for covering large areas of skin. In contrast to ointments, creams might cause allergic reaction due to the preservatives used.

***Pastes*:** like ointments, but stiffer, less greasy and applied thickly. e.g. Zinc Oxide.

***Gels*:** contain solid medications, like suspension, but in a thick liquid. They can be used both internally and externally. e.g. Aluminum hydroxide gel.

***Lotions*:** contain more water than creams. They are thus, thinner and penetrate into the skin more than creams. e.g. Calamine lotion.

Liquid dosage forms

Liquid dosage forms contain one or more active ingredients in a liquid vehicle such as solution, suspension or emulsion. Although fast acting and easier to adjust doses for pediatric patients, they are less stable than solid dosage forms, require preservatives, difficult to set accurate dose and mask the bitter taste or odor.

ι. Solution

A solution is an evenly distributed (homogenous) mixture of one or more dissolved medication (solute) in a liquid vehicle (solvent). They are classified based on vehicle by aqueous, alcoholic or hydroalcoholic solutions. Solutions can be used orally, parenterally or topically.

The most commonly used solutions include:

***Syrup*:** A preparation of medication in a concentrated aqueous solution of sugar, usually sucrose. If the sugar concentration is 85% w/v or more, it does not need preservatives.

***Elixir*:** A clear, sweet solution of medication in a hydroalcoholic solvent.

***Spirit*:** A hydroalcoholic solution that contains volatile and aromatic medication.

***Tincture*:** A hydroalcoholic solution that contains plant extracts.

***Solution for injection*:** it is a sterile, pyrogen-free, isotonic and buffered to physiologic pH aqueous solution containing medications. The aqueous vehicles mostly used for preparing injections are water for injection and Sodium Chloride Injection. Injections are available in sealed glass ampoules, prefilled syringes or prefilled infusion bags.

ιι. Dispersion

An emulsion is a dispersion of two immiscible liquids, usually oil and water, that do not mix together. One liquid is called the internal phase, and the other is called the external phase. It is a dispersion of oils in water with aid of an emulsifying agent. An emulsifying agent/ emulsifier (surfactant) is used to keep the two solvents together.

A Suspension is a finely divided, undissolved drug particles dispersed throughout a liquid vehicle in which the drug exhibits a minimum degree of solubility. There are two components in a suspension, the dispersed material and the dispersion medium. Pharmaceutical suspensions may be formulated to provide controlled drug delivery, e.g. as intramuscular or subcutaneous injections. Or increase duration of action e.g., Protamine Zinc-Insulin suspension

Suspension must be shaken before use.

Liniment is a medicated topical preparation for application to the skin. It is usually rubbed in to allow for penetration of the active ingredients. It is typically formulated from alcohol, acetone, or similar quickly evaporating solvents and contains counterirritant aromatic chemical compounds such as methyl salicylate, benzoin resin, menthol, or capsaicin. Liniments produce a feeling of warmth within the area they are applied to, typically acting as rubefacients via a counterirritant effect.

An *enema* is an injection of fluid into the lower bowel by way of the rectum. The most frequent uses of enemas are to relieve constipation and for bowel cleansing before a medical examination or procedure. They are also employed as a lower gastrointestinal series to treat traveler's diarrhea, as well as a vehicle for the administration of food, water or medicine.

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Inhalation dosage forms

These are aerosols, sprays, gaseous, vapors, powders, solutions or suspensions given via mouth or noses. The medications must be extremely fine to reach the site of action such as bronchial trees. Devices that facilitate delivery of this dosage forms are called vaporizers, humidifiers and nebulizers.

Aerosol is a spray that contains very fine liquid or solid drug particles in a gas propellant that is packaged under pressure.

Dose calculations

Proper dosing of medications is important to ensure patient safety. Giving medications in healthcare involves not only knowing what and when to give but also how much to administer. Dosing calculations are just as important as knowing what to give. Medications take many forms, but dispensing liquids are usually the hardest to calculate. Liquids and fluids come in different containers and concentrations but using simple mathematical calculations can simplify this task and lower the risk of potential errors [75,76].

α) **Dose, dosage and dosage regimen**

Dose, dosage and dosage regimens are mistakenly used as synonyms. However, there is a difference among these terminologies. While dose is specific quantity of a therapeutic agent to be administered in a given instance, or measured to be taken at one time; dosage is a broader term that represents both the size of the dose in question as well as the intervals at which the dose is to be taken. Dosage regimen is the scientific schedule based on patient characteristics that include a specific amount, number, and frequency of doses over a specific period of time.

β) **Units for doses**

Drug doses are expressed in conventional metric mass units (for example, milligrams or milligrams per kilogram). Moreover, certain drugs (such as insulin or heparin) may be prepared as mixtures and have no specific molecular weight, thereby precluding their expression in mass units. Although other drug dose units such as drops (for ophthalmologic preparations), grains (for aspirin), and various apothecary system measurements (e.g., teaspoonfuls, ounces, and drams) may be encountered clinically, these units generally are not used [76].

- 5 mL = 1 teaspoon
- 15 mL = 1 tablespoon
- 1mL = 20 drops
- 1 IU is equivalent to:
- 34.7 microgram (0.0347 milligram) of insulin
- 0.6 microgram (0.0006 milligram) of penicillin G
- 0.3 microgram (0.0003 milligram) of vitamin-A(Retinol)
- 0.6 microgram (0.0006 milligram) of vitamin-A(beta-carotene)
- 50 micrograms (0.050 milligram) of vitamin-C
- 25 nanograms (0.000025 milligram) of vitamin-D(cholecalciferol or ergocalciferol)
- 0.67 mg Vitamin E(d-alpha-tocopherol)
- 0.9 mg of Vitamin E(dl-alpha-tocopherol)

The term 'units' refers to International Units (IU,U), which is a measure of the "biological activity" of a specific drug, vaccines and vitamins. International Units are used over a conventional metric measure (such as milligrams) to make it easier to compare different forms of the same drug. The volume or mass that makes up one International unit is dependent on the concentration or potency of the substance and therefore varies from substance to substance depending on what is being measured. This means that converting between international units and micrograms or milligrams is not a simple calculation and we can't provide a converter to do this calculation for you. The exact measure of one IU of a substance is in fact established by international agreement for each substance. Essentially, the use of International Units is a way to standardize. It's incredibly uncommon to see insulin noted in milligrams (mg). They are always be labeled in units, or as a concentration in terms of units (e.g., U500 means 500 units of insulin per 1ml of liquid, U100 means 100 units of insulin per 1mL of liquid, U40 means 40 Units of insulin per 1mL of liquid). So, if you

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have a U100 insulin product, and you need to inject 50 units, that would come out to 0.5 mL. The syringe to be used also matters. For example, you cannot use U100 syringes if you are utilizing a U500 insulin product. Drawing up half-way, to 0.5 mL, on a U100 syringe will equal a dose of 50 units of U100 insulin. However, doing the same (drawing up to 0.5mL) with a U500 product would yield 250 units [75,76].

Pediatric dosing

While the adage that children are not small adults has existed for some time, most pediatric doses are still extrapolated from adult studies. Children experience large amounts of growth and development during early childhood which can dramatically affect the pharmacokinetics of different drugs. It is particularly difficult to predict pharmacological effects in neonates as development occurs quickly, resulting in rapid changes in drug metabolism over short periods of time which create difficulty in predicting doses. Thus, the capacity and functions of individual organs and the development of biochemical pathways are of greater importance. Nevertheless, there is a lack of pharmacokinetic studies in children of different ages. Traditional pharmacokinetic studies are hard to conduct in children and are subject to a greater range of ethical considerations. No mathematical method of dose estimation can replace clinical studies using actual outcomes, surrogate measures or therapeutic drug monitoring [76].

Many doses are based on the child's age or weight. Dosage regimens based entirely on age are often inaccurate and may lead to adverse effects, toxicity or lack of clinical effect. Weight-based dosing regimens are simple and are used in most clinical situations. However, with the lack of specific pediatric data, these dosing equations are often based on adult data and then scaled based on size and age as an approximation for drug activity in children. But, pediatric growth and development is not a linear process. Scaling from adult doses based on weight alone is not adequate for determining doses across the range of developmental processes that occur throughout childhood. An incorrect dose, particularly in neonates and infants, could have catastrophic adverse effects. It is good practice for two people to double check dose calculations, such as the prescriber and dispensing pharmacist. It may be adjusted according to the clinical response. Doses can be rounded to ensure they are able to be measured by parents and care givers accurately. Pediatric pharmacology developed initially from the extrapolation of therapeutic practice and experience in adults and the use of "scaled down" adult doses. This practice is clinically successful for the majority of drugs which are relatively non-toxic and have a wide margin between therapeutic and toxic doses. But, drugs with a narrow therapeutic margin, such as the aminoglycoside antibiotics and digoxin, require more sophisticated knowledge and individualized dosage regimens, of course, not only for children but in adults. Thus, concerted efforts into pediatric pharmacology research are required to ensure accurate selection of doses for children [45,76].

Pediatric formulas

Pediatric patients require special dosing that is adjusted for their age, body weight or body surface area (BSA). A number of formulas have been used throughout the years to determine the best dose for pediatric patients.

Age and weight based formulas

The three common formulas are Fried's, Young's and Clark's formulas. Fried's and Young's rules are based on age, whereas Clark's rule is based on body weight [76].

FORMULA **Pediatric Dosing**

Fried's Rule

$$\text{Child's dosage} = \frac{\text{Age in months}}{150} \times \text{Adult dosage}$$

Young's Rule

$$\text{Child's dosage} = \frac{\text{Age of child in years}}{\text{Age of child in years} + 12} \times \text{Adult dosage}$$

Clark's Rule

$$\text{Child's dosage} = \frac{\text{Child's weight in pounds}}{150} \times \text{Adult dosage}$$

Age based rules can be applied when the patient's weight is unknown. Fried's Rule is available to use to calculate an

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infant dosage for patients less than 24 months when a proper dosage has not been. Young's rule is used to calculate the proper dosage of medicine for children aged greater than 2 years.

Other rules based on age and body weight include Dilling's rule (age based), Cowling's rule (age based), Magid's rule (same as Clark's rule), Augsberger's rule (modification of Clark's rule), Bestedo's rule (age based) etc.

The other most commonly used method is mg/kg of body weight. This is used when the manufacturer recommends dosages for children based on body weight.

BSA based formulas

Pediatric dosing based on one's age has the potential for suboptimal therapeutic levels due to the broad range of potential weight, especially with increasing childhood obesity. Dosages based on the body weight are believed to be insufficient for the achievement of proper serum concentration of most drugs. However, calculations based on BSA offers better reliability compared to others since it based on two physical dimensions i.e. weight and height [76].

There are various BSA calculation methods. However, the most consistent and one is the Mosteller's formula for calculating BSA (m^2) = *square root of (height (cm) x weight (kg)/3600).*

Alternatively, BSA can be calculated from normogram chart. The patient's size is identified as BSA The average adult client (weighing 68-70kg) will have a BSA of $1.73M^2$. The normogram chart can be used to identify the patient's BSA based on their height and weight (cm and kg). The BSA is determined where a straight line connecting the patient's height and weight crosses over the BSA column. Once the BSA of the patient is determined the following formula can be used to calculate the correct Pediatric Dose: *Child's BSA in M^2 x Adult Dose/$1.73M^2$*.

Calculating IV flow rate and drop rate/drip rate

IV therapy fluids will come in sterile plastic bags or glass bottles. They may be infused by gravity using a manual roller clamp or dial-a-flow, or infused using an infusion pump. Regardless of the method, it is important to know how to calculate the correct IV flow rate. When calculating the flow rate, determine which IV tubing you will be using, microdrip or macrodrip, so you can use the proper drop factor in your calculations [75].

When using electronic infusion controllers, the flow rate needs to be set. The rate is the volume in ml divided by the duration in hours (mls per hour).

This calculation can be expressed as a formula- Flow rate = Volume (ml) / Time (hours)

When using manual infusion controllers, the drop rate needs to be set (drops per minute). This can be calculated using the following formula-

Drop rate = Drop factor x Volume/60 x Time (hours)

The drop factor is the number of drops (gtts) in one mL of solution, and is printed on the IV tubing package.

There are two standard tubings:

1. Macro Drop Factor — drop size is normally 10-20 drops in 1mL.
2. Micro Drop Factor — drop size is normally 60 drops in 1mL.

Macrodrip and microdrip refers to the diameter of the needle where the drop enters the drip chamber. Macrodrip tubing is used to infuse large volumes or to infuse fluids quickly. Microdrip tubing is used for small or very precise amounts of fluid, as with neonates or pediatric patients.

Routes of drug administration

The route of administration is determined by properties of the drug (for example, water or lipid solubility, ionization) and by the therapeutic objectives (for example, the need for a rapid onset, the need for long-term treatment, or restriction of delivery to a local site). Major routes of drug administration include enteral, parenteral, inhalation and topical, among others [42-45].

Enteral routes

Enteral routes, administration along alimentary tract, include Oral (Per Os-PO, sublingual, buccal) and rectal. Rectal administration allows absorption of drugs through rectal mucosa [44].

***PO*:** Generally, it is the safest and most common, convenient, and economical method of drug administration. The

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drug may be directly swallowed or swallowed after chewing. This route provides many advantages i.e. easily self-administered, and toxicities and/or overdose may be overcome with antidotes, such as activated charcoal. However, there is slow onset and the pathways involved are the most complicated, and hostile. GIT and liver are rich with microsomal enzymes (CYP450) and there is high probability of first pass metabolism as a result. Besides, the low gastric pH might inactivate some drugs.

***Sublingual/buccal*:** The drug is placed under the tongue for sublingual, or between the gums and cheek for buccal. These routes have several advantages, including ease of administration, rapid absorption, bypass of the harsh gastrointestinal (GI) environment, and avoidance of first-pass metabolism. But, it is not suitable for large dosage forms.

***Rectal*:** Because 50% of the drainage of the rectal region bypasses the portal circulation, the biotransformation of drugs by the liver is minimized with rectal administration. The rectal route has the additional advantage of preventing destruction of the drug in the GI environment. This route is also useful if the drug induces vomiting when given orally, if the patient is already vomiting, or if the patient is unconscious. Rectal absorption is often erratic and incomplete, and many drugs irritate the rectal mucosa.

Parenteral routes

A parenteral route allows administration of drugs through injection into the systemic circulation. It is used for drugs poorly absorbed from GIT, gastric unstable drugs, uncooperative patients and during emergency. Parenteral routes have the highest bioavailability. Moreover, the most control is possible over the actual dose of drug delivered to the body. Nevertheless, it is irreversible and may cause pain, fear, local tissue damage, and infections [45].

The three major parenteral routes are intravascular (intravenous or intra-arterial), intramuscular, and subcutaneous.

Intravenous (IV): The most common and permits rapid effect and maximum degree of control over the amount of drug delivered. It is also important for irritant drugs. There are two forms, *IV bolus* where the full amount of drug is delivered immediately and *IV infusion* where fixed dose is infused over a longer period of time. Large parenteral fluid can also be given.

Patients must be carefully monitored for drug reactions, and the rate of infusion must be carefully controlled. The formulation for IV administration is called ampoule and requires strict aseptic procedures. It must be aqueous solution; oily solution or any form suspension should not be given through IV.

Once administered, it would be difficult to reverse. Moreover, there is risk of contamination at the site of injection, may induce hemolysis, or cause other adverse reactions if the medication is delivered too rapidly and high concentrations are reached too quickly.

Intramuscular (IM): it permits administration of drugs into gluteal and deltoid muscles. Both aqueous and oily solutions as well as suspensions can be given through IM. Specialized or depot preparations, which are absorbed slowly, can also been given. Depot preparations often consist of a suspension of the drug in a non-aqueous vehicle such as polyethylene glycol. As the vehicle diffuses out of the muscle, the drug precipitates at the site of injection. The drug then dissolves slowly, providing a sustained dose over an extended period of time.

IM is not suitable for large parenteral fluid administration.

***Subcutaneous (SC)*:** provides constant, slow, and sustained effects. This route should not be used with drugs that cause tissue irritation, because severe pain and necrosis may occur.

***Intrathecal/ intraventricular*:** Introduce drugs directly into the cerebrospinal fluid.

- Intra-articular
- Intra-arterial
- Intraperitoneal
- intradermal

Inhalation (Pulmonary) route

The pulmonary or inhalation route allows provides rapid delivery of powdered, aerosolized liquid and gaseous formulations through oral and nasal cavity into the large surface area of the mucous membranes of the respiratory tract. Effects are almost as rapid as those with IV [45].

Topical

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Topical route allows direct application on site of problem.

Transdermal: application of drugs to the skin, usually via a transdermal patch

Drug supply management

Supplying drugs: Drugs are vital components of patient care all over the world. They represent a large part of the public health budget. While there are large numbers of drugs are available in market, funds to secure them are generally limited. Besides, it is difficult to keep up-to-date information with all the drugs on the market. Thus, there should be efficient drug supply management that is governed by a policy. Ethiopia has a national drug policy aimed to ensure adequate supply of medicines which are required for treatment of diseases affecting the majority of the country's population, which gives the primary mandate to the government. To achieve this, the country developed national list of essential medicines which guides the decision of all health service providers with regard to selecting and availing the most needed medicines at every level of the healthcare system at all times with affordable cost [77-79].

Drugs supply management is a highly technical and professional activity that can only be achieved by suitably qualified, adequately trained, sufficiently skilled man power both at managerial and ground level. The management of drug supply is grossly organized around five basic functions of the Medicines Management cycle namely, selection, quantification, procurement, storage and use. Appropriate measures need to be taken in the forms of decisions, actions to make the supply chain more robust and efficient. At the center of this cycle is a core of management support systems, which include organization, financing and sustainability, information management, human resource and quality assurance management [78].

Selection

The selection of pharmaceuticals is a basic and extremely important professional function of the suitably qualified and well-trained pharmacist who is charged with making decisions regarding products, quantities, product specifications, and sources of supply. Price, terms, shipping times, dependability, quality of service, returned goods policy, and packaging must be considered during selection. Bedrock of drug selection has to be the Essential Drugs List/ Essential Medicine List. The process of selecting essential drugs for a particular health system will not satisfy and reflect the needs of the users or be accepted by them unless the process is consultative and transparent; the selection criteria are explicit; selection process is linked to evidence-based clinical guidelines; and the lists are divided into levels that are regularly reviewed and updated. Clinical guidelines along with essential drugs list should be reviewed at least every two to three years, and their use and the impact should be monitored on regular basis.

Quantification

Quantification is a key function in health commodity management and it refers to the process of estimating needs for quantities of specific health commodities during a specific period of time. Accurate quantification requires information from various sources. These include the EDL, consumption data, epidemiological (morbidity) data, prescription patterns, minimum and maximum stock levels, frequency of stock-outs, and length of the procurement cycle. All these elements make quantification a complicated exercise, which is highly vulnerable to mistakes. Even when quantification is done accurately, the ability of a health system to ensure a full supply pipeline can be limited by the funds available to health facilities for purchasing required items.

Eliminating wastage is predicated upon effective inventory and forecasting management, which deals with requirement estimation, analyzing consumption patterns and forecasting demand.

Procurement

Timely supply of drugs, medical supplies and equipments of good quality, which involves procurement as well as logistic management, is of critical importance in any health care system. Legal, policy and regulatory environment are recognized as providing an important foundation for public procurement in the health sector. A robust procurement policy should have an integrated approach starting from preparation of an essential drugs list; assessment of the quantity of drugs needed; quality assurance from suppliers; procurement process; supply chain management and prompt payment to suppliers.

Existing government policies, rules and regulations for procurement as well as institutional structures are frequently inadequate and sometimes hinder overall efficiency in responding to the modern pharmaceutical market. The regulatory system in particular as far as public procurement in the health sector is concerned has been relatively weak.

Storage

Proper environmental controls like proper temperature, light, humidity, conditions of sanitation, ventilation and segregation must be maintained wherever drugs and supplies are stored. It is extremely important to have warehouses with sufficient storage space, fitted with heavy-duty racking system to avoid wastage of space along with pallets, hydraulically operated hand-trolleys and pedestrian controlled electric stackers to handle the medicines scientifically and efficiently. Storage areas must be secure; fixtures and equipments used to store drugs should be constructed so that drugs are accessible only to designated and authorized personnel. Such personnel must be carefully selected and supervised. Safety is an important factor, and proper consideration should be given to the safe storage of poisons and inflammable compounds [80].

Additionally, the desired stock level of specific products or items must be maintained i.e. efficient inventory management is needed. Pharmacy inventory management is a complex but critical process within the health care delivery system. Without adequate pharmacy inventory management practices, health care facilities run the risk of not being able to provide patients with the most appropriate medication when it is most needed. Addressing pharmacy inventory management and the revenue cycle effectively can enable organizations to improve financial performance, adhere to regulatory requirements, reduce risks relating to patient safety, and ensure availability of drugs without frequent stock outs. Many organizations utilize pharmacy management systems as a means of ensuring appropriate accountability over pharmaceuticals and ensuring the traceability of inventory from purchase through administration to the patient or disposal level. Effective and transparent tracking systems that allow pharmacies to accurately record inventory components, such as medication expiration dates and physical quantities, also have the potential to reduce adverse patient outcomes. Along these, bin cards and stock cards are used. There is standardized inventory management tools used in inventory management. These are bin card, stock card, Internal Facility Request and Resupply form (IFRR), Report and Requisition Form (RRF). The bin card (blue card) is kept with the product inside the store and up dated in every transaction while stock card (yellow card) is similar to the bin card but is used to track stock based on issuing and receiving orders. There should not be discrepancies between card balances and physical balances (after on-the-spot physical counts) at all levels. The IFRR voucher is used to report internal transfer of items between the facility's pharmaceutical store and dispensing units. The RRF is used to order health commodities from Supply agencies like Ethiopian Pharmaceutical Supply Agency/EPSA (the former PFSA/ PHARMID /EPHARMCORE) whereas RRUC is used to track the transfer of supplies back to EPSA. Normally, availability of essential medicines should be 100%, but it is not the case practically [81].

Distribution and use

The primary drug distribution management goal is to maintain a steady supply of pharmaceuticals and supplies to facilities where they are needed, while ensuring that resources are being utilized in the most effective manner. Distribution costs, which include costs related to storage and transportation, are a significant component of the expense of running a public health supply system. Effective pharmaceutical distribution relies on good system design and good management. Adequate and dedicated transportation facilities laced with cold chain maintenance are an important factor in maintaining timely distribution of quality medicines round the clock at health facilities. An efficient drug distribution system ensures availability of the right medicines in sufficient quantities procured at the lowest prices to secure the maximum therapeutic value to the largest number of beneficiaries with the available and additional resources. Efficient distribution management includes the availability of an efficient network of storage facilities, keeping reliable records of drug stock balance and consumption, maintaining accountability procedures, ensuring adequate and secured storage, reliable transport systems and reinforcing, reporting and supervisory practices [78].

Expiry date (Shelf-life) of drugs

The idea that drugs expire on specified dates goes back at least a half century, when the FDA began requiring manufacturers to add this information to the label. To determine a shelf life, drugs are exposed to intense heat and soaked with moisture to see how it degrades under stress. The drug company proposes a scientifically studied shelf-life that must be reviewed and approved by FDA.

Drug expiry date must exist on all drugs. Drug expiry dates reflect the time period during which the product is known to remain stable, which means it retains its strength, quality, and purity when it is stored according to its labeled storage conditions. It is the final day that the manufacturer guarantees the full potency and safety of a given drug. Shelf-life is the period of time, from the date of manufacture, that a drug product is expected to remain within its approved product specification while stored under defined conditions. It reflects the time where a product will work both safely and effectively. The amount of time a product can stay stable under certain environmental conditions, equates to its shelf life. The phrase "shelf life" and "expiry date" is often used interchangeably, as both terms reflect the same concept:

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there is a period of time where a product is stable and safe for use. The shelf-life of a drug is estimated using stability testing under GMP. That is why "shelf life testing" is also referred to as "stability testing" [78].

Most drug products have a shelf-life between 12 to 60 months from the time of manufacturing. Shelf-life depends on the type of dosage forms. For example, solid dosage forms, such as tablets and capsules, appear to be most stable compared to others. Moreover, all the drugs must be in their original sealed containers. Once the original container is opened or when the drug is repacked the expiry date is no longer guaranteed. Defiance to the storage conditions could also negatively affect the shelf-life of a given drug. The appropriate conditions will depend on the drug, but may include considerations regarding temperature, humidity, and exposure to light. Proper storage of medications may help to extend their potency. For example, solid medications remain most stable in dry, cool spaces away from light. Additionally, instructions for refrigeration or freezing must be carefully followed.

Shelf-life testing/Stability testing

Shelf-life testing of a drug product is a means of assessing the functionality, effectiveness, and stability of a pharmaceutical product over a period of time to either establish a new expiry date for a new product, or to collect data in ongoing support of an already-existing expiry date for a commercial/marketed product. To challenge the lifespan of either a new or commercial drug product, it is exposed to various extremes of regulated temperature and humidity conditions for specified lengths of time, inside what are known as "stability chambers". At periods throughout the study, known as "time points", samples are removed from their storage conditions, and their integrity is assessed by conducting laboratory testing against an approved, stability product specification. "Time points" reflect the duration of time that the product has been exposed in the set temperature/humidity storage condition. Usual time points for testing are at 0, 3, 6, 9, 12, 18, 24, 36 months, etc. It is referred as "accelerated" because high temperature/humidity exposure to the product over a short period of time accelerates product degradation. In other words, it stresses and challenges the product's chemical composition to the extreme [45].

There's really no way to know if a drug is safe unless it is tested for potency. However, healthcare systems can assess physical characteristics of a given drug. These include evaluation of the packaging/closure system, product color, odor, hardness, dissolution, disintegration, pH, viscosity, etc. Drugs that exist in solution, especially injectable drugs, should be discarded if the product forms a precipitant or looks cloudy or discolored.

Health hazards of expired drugs

FDA never recommends taking drugs beyond their expiration date as it is risky with many unknown variables. At the pharmacy, "beyond-use" dates must be put on the prescription bottle label given to the patient. These dates should say "do not use after." or "discard after." and are required both legally as well as ethically. These dates are typically one year from the date of fill. Laws prohibit pharmacists from dispensing expired drugs and necessitate facilities to remove expired medication from their supply. Outdated drugs are shunted to shelves in the back of the pharmacy and marked with a sign that says: "Do not dispense." The piles grow for weeks until they are hauled away by a third party company that has them destroyed [78].

Loss of strength is a primary concern since it is associated with treatment failure. That being said, it's an open secret among medical professionals that many drugs maintain their ability to combat ailments well after their labels say they don't. Although difficult to know which product could have an extended shelf life, many drug products may have extended shelf lives beyond their expiration date. Many professionals question the expiration dates on most drugs. They feel that it should be standard to make sure drugs that are still effective aren't thrown away. They have pushed for a changed approach to drug expiration dates-with no success. Of course, the shelf life of many drugs seems to be "considerably longer" than their proclaimed expiry dates, leading to "unnecessary waste, higher pharmaceutical costs, and possibly reduced access to necessary drugs for some patients."

The second concern is that a given drug might degrade into toxic components and could harm patients. However, there is no tangible report so far about anyone being injured by drugs used beyond expiry dates. In 1963, a report that tied degraded tetracycline use with a form of renal tubular (kidney) damage known as "Fanconi Syndrome" was published. However, many medical experts question the results of this case report [45].

Extended shelf-life

Though the FDA requires pharmacies to throw away expired drugs, it doesn't always follow these instructions itself. The US federal agencies that stockpile drugs — including the military, the Centers for Disease Control and Prevention and the Department of Veterans Affairs — have long realized the savings in revisiting expiration dates. In 1986, the Air Force, hoping to save on replacement costs, asked the FDA if certain drugs' expiration dates could be extended.

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In response, the FDA and Defense Department created the Shelf Life Extension Program. Each year, drugs from the stockpiles are selected based on their value and pending expiration and analyzed in batches to determine whether their end dates could be safely extended. For several decades, the program has found that the actual shelf life of many drugs is well beyond the original expiration dates. Under the Shelf-Life Extension Program (SLEP), FDA conducts testing for certain products stored in federal stockpiles in environmentally controlled locations. The extension program could work for drugs stored in pharmacies if they are properly stored i.e. stored in stable conditions similar to the national stockpile. However, drugs held by healthcare providers and consumers may have been stored under varied conditions after entering the market. As a result, it would be difficult to test and extend shelf-life in a similar manner [42-45,78].

Most drug manufacturing companies are not happy with SLEP. They would rather sell new drugs and develop additional products than dealing with drugs in market. They ring up more sales when medications are tossed as "expired".

Drug disposal

Drugs waste is a public safety concern, resulting in a possible accidental poisoning, misuse, and environmental pollution. Global concerns associated with improper drug disposal include inappropriate self-medication, accidental consumption by children, accumulation of active ingredients in streams as environmental pollutants, a risk of antimicrobial resistance, and accidental poisoning. Thus, appropriate disposal of the damaged and expired medicines would save lives and protect the ecological system. Medicines which are unfit for use shall not be stored for more than six months. Disposal of drug wastes shall be accompanied with lists of products to be disposed clearly stating trade name and/or generic name, strength (where applicable), dosage form, pack type and size, quantity, batch number, expiry date, manufacturer, supplier, country of origin, and product price.

Drug waste includes both hazardous and non-hazardous waste, controlled substances, and expired pharmaceuticals. Medication waste can come from multiple levels in the drug's lifespan. First, it can come from production factories from where they were created. This includes unwanted pharmaceutical ingredients and materials that can no longer be used in the drug manufacturing process. Second, medication waste can be generated from healthcare facilities including hospitals, clinics, and pharmacies. Medication waste from this source can be from over prescribing of drugs from healthcare providers, hospital labs, expired drugs, opened drug containers and partially used medications. Furthermore, these wastes can include materials, such as syringes, vials, IV bags, and tubing that contain excess drugs or contaminated in the process of handling hazardous pharmaceuticals, such as chemotherapy drugs [82-84].

Drug waste disposal methods

Constraints in funding for disposal of waste pharmaceuticals necessitate cost-effective management and methods. The main way to achieve this is to sort the material to minimize the need for expensive or complicated disposal methods.

Return to donor or manufacturé

Wherever practical the possibility of returning unusable drugs for safe disposal by the manufacturer should be explored; particularly drugs which present disposal problems, such as antineoplastics. For unwanted, unrequested donations, especially those that arrive past or unreasonably near their expiry date it may be possible to return them to the donor for disposal.

Cross-frontier transfer of pharmaceutical waste.

Landfill

Landfill is the oldest and the most widely practiced method of disposing of solid waste. It is the method where drug waste is directly placed into a land disposal site without prior treatment or preparation.

Three types are recognized.

- ***Open uncontrolled non-engineered dump*:** probably the most common land disposal method in developing countries. Untreated waste discharged into an uncontrolled, non-engineered open dump does not protect the local environment and should not be used. Discarding of untreated waste pharmaceuticals into such a site is not recommended except as a last resort.
- ***Engineered landfill*:** such a landfill has some features to protect from loss of chemicals into the aquifer.
- ***Highly engineered sanitary landfill:*** properly constructed and operated landfill sites offer a relatively safe disposal route for municipal solid wastes, including waste pharmaceuticals. The term "safe sanitary landfill" refers to

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such a site that is adequately situated, constructed and managed.

Waste immobilization

Encapsulation: Involves immobilizing the pharmaceuticals in a solid block within a plastic or steel drum. Drums should be cleaned prior to use and should not have contained explosive or hazardous materials previously. They are filled to 75% capacity with solid and semi-solid pharmaceuticals, and the remaining space is filled by pouring in a medium such as cement or cement/lime mixture, plastic foam or bituminous sand. For ease and speed of filling, the

Inertization: Involves removing the packaging materials, paper, cardboard and plastic, from the pharmaceuticals. Pills need to be removed from their blister packs. The pharmaceuticals are then ground and a mix of water, cement and lime added to form a homogenous paste. The paste is then transported in the liquid state by concrete mixer truck to a landfill and decanted into the normal urban waste. The paste then sets as a solid mass dispersed within the municipal solid waste.

Sewer

Some liquid pharmaceuticals, e.g. syrups and intravenous fluids, can be diluted with water and flushed into the sewers in small quantities over a period of time without serious public health or environmental affect. Fast flowing watercourses may likewise be used to flush small quantities of well-diluted liquid pharmaceuticals or antiseptics.

Burning in open containers

Pharmaceuticals should not be destroyed by burning at low temperature in open containers, as toxic pollutants may be released into the air. Paper and cardboard packaging, if they are not to be recycled, may be burnt. Polyvinyl chloride (PVC) plastic however must not be burnt.

Incineration

ι. ***Medium temperature incineration****:* Shall be of double chamber design which operates at a medium-temperature combustion process (850-1,000^{0}C) with a combustion retention time of at least two seconds in the second chamber.

ιι. ***High-temperature incineration*****:** Shall be of double chamber design which operates at a temperature combustion process in excess of 1,200^{0}C with a combustion retention time of at least two seconds in the second chamber. High-temperature incinerators shall be fitted with gas cleaning equipment.

In both cases (I & ii) the final ash shall not be left to open air. It shall be collected and dumped into landfill which appropriate bodies have participated at selecting.

EPSA has been establishing incineration centers at Adama, Mekele, Bahir Dar, Dessie, Jima, Neqemte, Hawasa and the city of Dire Dawa. The incineration centre to be established in Adama will have a capacity of burning 1,000kg of medical waste an hour, while the rest will burn 500kg of waste an hour. The incinerators are pyrolytic incinerators comprised of pyrolytic chambers where the waste is thermally decomposed through an oxygen deficient, medium-temperature combustion process in a 800-900 degree chamber. The incinerators in the post-combustion chamber minimize smoke and odours using an excess of air heated 900– 1200 degrees centigrade. The center at Adama has already been functional.

Chemical decomposition

If an appropriate incinerator is not available, the option of chemical decomposition can be used in accordance with the manufacturer's recommendations, followed by landfill. This method is not recommended unless chemical expertise is readily available. Chemical inactivation is tedious and time consuming, and stocks of the chemicals used in treatment must be made available at all times. For disposal of a small quantity of antineoplastic drugs this method may be practical.

Medicines waste disposal team

The team shall have the following professionals:

α. Pharmacist,

β. Environmental health professional,

χ. Sanitary Engineer (for landfill only)

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δ. Security and other administrative staff for the disposal site.

Improper disposal

Improper disposal may be hazardous if it leads to contamination of water supplies or local sources used by nearby communities or wildlife. Expired drugs may come into the hands of scavengers and children if a landfill is insecure. Pilfering from a stockpile of waste drugs or during sorting may result in expired drugs being diverted to the market for resale and misuse. Most pharmaceuticals past their expiry date become less efficacious and a few may develop a different adverse drug reaction profile. There are some categories of expired drugs or defective disposal practices that carry a public health risk.

The pharmaceutical sector in Ethiopia is dominated by imports although a small portion of the needs are covered by local manufacturing. There are malpractices with regard to pharmaceutical waste management by these sectors. Although, importers and factories generate both hazardous and non-hazardous waste, most of them are unaware of the country policies and regulations in handling such wastes. Even those that are aware are not adhering to these policies and regulations. Moreover, environmentally unfriendly ways of pharmaceutical waste disposal such as land fill and open air burning are common. Besides, most pharmaceutical industries directly release their waste to the effluent system. Majority of private drug retail outlets also dispose unused or expired medicines inappropriately. To tackle such challenges, a need to train personnel in industries, importers and regulatory authorities about safe disposal of pharmaceutical wastes is urgently needed thus safe medicines waste disposal can be practiced in the country [80].

The following precautions should be taken:-

- Contamination of drinking water must be avoided.
- Landfills must be sited and constructed in a way that minimizes the possibility of leachate entering an aquifer, surface water or drinking water system.
- Non-biodegradable antibiotics, antineoplastics and disinfectants should not be disposed of into the sewage system as they may kill bacteria necessary for the treatment of sewage.
- Large quantities of disinfectants should not be discharged into a sewerage system or watercourse but can be introduced if well diluted.
- Burning pharmaceuticals at low temperatures or in open containers results in release of toxic pollutants into the air. Ideally this should be avoided.
- Inefficient and insecure sorting and disposal may allow drugs beyond their expiry date to be diverted for resale to the general public.
- In the absence of suitable disposal sites and qualified personnel to supervise disposal, unwanted pharmaceuticals present no risk provided they are securely stored in dry conditions. If stored in their original packing there is a risk of diversion and to avoid this they are best stored in drums with the pharmaceuticals immobilized.

Rational drug use

Rational drug use (RDU) is about "patients receiving medications appropriate to their needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community". Rational use of drugs will maximize the therapeutic outcomes, reduce adverse drug reactions and drug interactions, shorten the duration of hospital stay and decrease the healthcare costs of patients and settings. The five important criteria for rational drug use are accurate diagnosis, proper prescribing, correct dispensing, suitable packing and patient adherence. The prescribers should make an accurate diagnosis and prescribe rationally and the pharmacist should ensure that effective form of the drug reaches the right patient in prescribed dosage and quantity, with clear instructions on its appropriate use. The pharmacist is often the last member of the health care team to see the patient before he/she takes the drug and has an immense responsibility in counseling the patients. The introduction of clinical pharmacy practice enables pharmacists to provide trusted drug information services to other healthcare providers, including prescribers. Moreover, there is a possibility for pharmacist's prescribing for limited drugs. Among the various measures, the development and revision of National essential drug list, development of National Formulary, promoting pharmaceutical care, strengthening drug and therapeutics committee (DTC) and opening drug information centers are vital [42-45].

Rational drug use can partly be achieved when there is a rational prescribing of drugs with generic or non-proprietary name and from an Essential Drugs List (EDL) of the healthcare setting (if any) or from the country at large. Drugs prescribed with generic name can also increase the availability and affordability of drugs. World Health Organization

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(WHO) has designed standardized core prescribing and patient care indicators to evaluate the trends of drug use in outpatient settings of health facilities. Each core indicators have five components. The prescribing indicators include the degree of polypharmacy, the percentage of drugs prescribed with generic name, the percentage of encounters with at least one antibiotic and injection and the percentage of drugs prescribed from EDL. Moreover, the patient care indicators include, average consultation time, average dispensing time, percentage of drugs actually dispensed and labeled as well as the percentage of patients' who know how to take the correct dosage. The recommended value of WHO for core prescribing indicators include: average number of drugs per encounter <2(1.4-1.8), percent encounters with antibiotics <30% (20-26.8%), and percent encounters with injection(s) <25% (13.4-24.1%), whereas ideally adopted value for prescribing by generic name and from EDL is 100% each. Coming to the WHO patient care indicators, the average consultation time (>10 min), average dispensing time (>180 s), and the percentage of drugs actually dispensed, labeled and patient knowledge are all ideally 100% [85].

These indicators measure the performance of prescribers and dispensers in key areas concerning rational drug use. The indicators assess prescribing, dispensing and patient use of drugs based on clinical encounters at healthcare facilities for the treatment of different illnesses. These indicator studies are less useful when used for inpatient care.

Prescription

Historically, prescriptions were written in Latin and are still written that way today. The word prescription itself comes from the Latin word *praescriptus*. It has the prefix *pre-*, which means "before," and the term *script*, which means "writing," indicating that a prescription, has to be written before a drug is compounded. *Rx* is a universal symbol to indicate a prescription. The origin of *Rx* as an abbreviation for "prescription" has been attributed to the Latin word "recipe," which means "take" [42-45].

A prescription contains instructions for the dispensing and administering of medications. It has five main sections:

- **Superscription**: This heading includes the date and the patient's name, address, age, and other important information.
- **Symbol Rx**: It's the universal symbol for "prescription."
- **Inscription**: This is the information about the medication itself. It has the name of the ingredients and the amount needed. It includes the main ingredient, anything that helps in the action of the drug, something to modify the effects of the main drug, and the vehicle which makes the medicine more pleasant to take.
- **Subscription**: The subscription section tells the pharmacist how to dispense the drug. This will have instructions on compounding the drug and the amount needed.
- **Signature**: The signature has the directions that are to be printed on the medicine. The word *sig* means "write on label."

Not all drugs require prescription. There are three categories of drugs

1. Over-the-counter (OTC) drugs: drugs are available in pharmacies and supermarkets without special restrictions;
2. Behind-the-counter drugs: drugs that are dispensed by a pharmacist without needing a prescription;
3. Prescription only drugs: drugs that must be prescribed by a licensed physician. In the United Kingdom, behind-the-counter medicines are called pharmacy medicines. These medications are designated by the letter P on the label.

The range of medicines available without a prescription varies from country to country. In Ethiopia, drugs are classified into two, as OTC and prescription only. Both categories are available in drugs stores and pharmacies only. Supermarkets are not allowed to hold drugs in Ethiopia; some dermatological preparations are sometimes observed in supermarkets and cosmetic shops. This is unquestionably an illegal practice.

Medical abbreviations on pharmacy prescriptions

Odd encrypted medical abbreviations are still used on prescription. They are known as apothecary prescription abbreviations. Some are derived from the Latin through its historical use in medicine and pharmacy, whereas others have evolved through prescribers' use of writing shortcuts [41-44].

Misinterpretation due to these abbreviations, is one of the most common and preventable causes of medication errors. Thus, they should be used with caution in the healthcare setting. Even some of the typed or computer-generated abbreviations, prescription symbols, and dose designations can still be confusing and lead to mistakes in drug dosing or

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timing. In addition, when these abbreviations are unclear, extra time must be spent by pharmacists or other healthcare providers trying to clarify their meanings, which can delay much-needed treatments. Some drug names are also abbreviated. For example, most antiretroviral drugs, anti-TB drugs, anticancer drugs and some antibiotics are often abbreviated. There are still abbreviations for dosage forms such as modified-release types (e.g. ER for extended release; SR for sustained release).

Health professionals should be very familiar with the abbreviations used in medical practice and in prescription writing. All drug names, dosage units, and directions for use should be written clearly to avoid misinterpretation. The use of a controlled vocabulary, a reduction in the use of abbreviations, care in the writing of decimal points, and the proper use of leading and terminal zeros have been urged to help reduce medication errors. Over the years, prescribers have developed many conventions for prescription-writing, with the goal of avoiding ambiguities or misinterpretation. The best way is to avoid such abbreviations altogether [85].

Doctor's handwriting

Doctors' handwriting is a reference to the stereotypically illegible handwriting of some medical practitioners, which sometimes causes mistreatment. In the US, illegible handwriting has been indirectly responsible for at least 7,000 deaths annually. There are several theories about the causes of this phenomenon. Some sources say it is related to workload; others claim that doctors neglect proper handwriting due to medical documents being intended to be read solely by medical professionals, not patients; still others simply classify the handwriting of doctors as a Handwriting style. The issue may also have a historical origin, as physicians have historically used Latin words and abbreviations to convey prescriptions; many of the abbreviations are still widely used in the modern day and could be a source of confusion. Some jurisdictions have legislatively required prescriptions to be legible, and some organizations have advocated the elimination of handwritten prescriptions altogether. In Ethiopia, there are instances where pharmacists could not successfully read Doctor's handwriting. It is even taken as lack of knowledge by some, which is not true.

Generic substitution

Many brand name drugs have cheaper generic drug substitutes that are therapeutically and biochemically equivalent. Prescriptions will also contain instructions on whether the prescriber will allow the pharmacist to substitute a generic version of the drug. This instruction is communicated in a number of ways. In some jurisdictions, the preprinted prescription contains two signature lines: one line has "dispense as written" printed underneath; the other line has "substitution permitted" underneath. Some have a preprinted box "dispense as written" for the prescriber to check off (but this is easily checked off by anyone with access to the prescription). In Ethiopia, generic substitution is not allowed at pharmacy level if it is written with brand names. Generic drugs are not easily welcome in Ethiopia since there is fear of fake drugs (counterfeit, substandard, adulterated etc). This fear is only related to imported drugs, and by now there is better trust on domestically produced drugs. Such fear can only be avoided through strong regulatory system, which is not at the required level currently [86].

In some cases, drug companies or their promoters use direct-to prescriber advertising in an effort to convince prescribers to dispense as written with brand name products rather than generic drugs.

Medication error

A medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing, order communication, product labeling, packaging, and nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use [85,86].

Thousands of prescription only and countless OTC drugs are available in health care settings. It is conceivable that mistakes can be made when practitioners prescribe or dispensers dispense drugs. Added to this is the high risk of interaction between substances. There are also thousands of nutritional supplements, herbs and potions. Over 80% of Ethiopians use traditional medicines, either alone or in combination with modern drugs. Additionally, hundreds of thousands of other patients experience but often do not report an adverse reaction or other complication related to a medication. Patients experience monetary cost, psychological and physical cost as a result of medication errors. Besides, a major consequence of medication errors is that it leads to decreased patients satisfaction and a growing lack of trust in the healthcare system.

Medication errors can occur at many steps in patient care, from the point of ordering the medication to the time when the patient is administered the drug. However, the most common one occurs at the prescribing stage. Typical

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errors include the healthcare provider writing the wrong medication, wrong route or dose, or the wrong frequency. These ordering errors account for almost 50% of medication errors. Data show that nurses and pharmacists identify anywhere from 30% to 70% of medication-ordering errors. It is obvious that medication errors are a pervasive problem, but in the majority of cases, the problem is preventable.

Strategies to prevent medication errors

Using legible writing: Illegible writing has plagued both nurses and pharmacists for decades. Physicians are often in a hurry and frequently scribble down orders that are not legible; this often results in major medication mistakes. Pharmacists and nurses should never take a guess at what the drug/dose is. This problem can be been resolved with careful writings or the use of electronic typing.

***Writing down the precise dosage*:** Distortion of dose can easily occur when nonspecific abbreviations or decimal points are used without thought.

***Using metric measures*:** The use of apothecary measures are now part of the historical archives; weight measures like grains, drams, and minims have little meaning to the modern day healthcare workers and should no longer be used. Instead, the universal metric measures should be used. When using metric measures, use of the decimal point must be done with care.

***Using abbreviations*:** One very common cause of medication errors is the use of abbreviations. Additionally, these abbreviations can have several other meanings and can be misinterpreted. It is recommended that abbreviations not be used at all when writing medication orders.

***Considering patient age*:** The two populations that are very sensitive to medications are the elderly and children. The patient's age and body weight should always be checked to ensure that the dose calculation is correct.

***Considering liver and kidney function*:** Another very common reason for medication errors is not taking into account renal or liver failure. Patients with renal and liver dysfunction need lower doses. Otherwise, toxicity can result because of the failure to excrete or break down the medication.

***Approaching every prescription with caution*:** Today generic drugs with similar names have flooded the market. In addition to having similar names, many of these medications have multiple uses and alternative names. If the diagnosis is not stated on the prescription, there is a risk that the drug may be prescribed for too long or an inadequate amount of time. Thus, high caution is required.

***Keeping drugs in their original containers*:** Many pills look alike, so keeping them in their original containers will help know the name of the drug and how to take them.

Generally, reducing medication errors requires open communication with the patient and the pharmacist. Writing prescriptions is an everyday part of the job in healthcare settings. However, the increased demands to see more patients who require many medications often become monotonous, and one can become careless. The majorities of healthcare workers never anticipate an adverse drug event, and consequently, rarely check back with the pharmacists for drug interactions. Though there is no single way to eliminate all drug errors, healthcare workers can reduce the errors by becoming more cautious and interacting closely with other practitioners, pharmacists, and patients. Open and direct communication is one way to bridge the safety gap [85,86].

The five rights of medication administration

One of the recommendations to reduce medication errors and harm is to use the "five rights": the right patient, the right drug, the right dose, the right route, and the right time. The five rights should be accepted as a goal of the medication process not the "be all and end all" of medication safety. The five rights focus on individual performance and not on human factors and system defects that may make completing the tasks difficult or impossible [85].

1. Right patient

- Check the name on the order and the patient.
- Ask the patient to identify himself/herself.

2. Right drug

- Check the order
- Check the medication label

3. Right dose
- Check the order
- Confirm appropriateness of the dose using a current drug reference.
- If necessary, calculate the dose and have another nurse calculate the dose as well.

4. Right route
- Again, check the order and appropriateness of the route ordered.
- Confirm that the patient can take or receive the medication by the ordered route.

5. Right time
- Check the frequency of the ordered medication.
- Double-check that you are giving the ordered dose at the correct time.
- Confirm when the last dose was given.

Consequences of medication error

- Death
- Life threatening situation
- Hospitalization
- Disability
- Birth defect

Removal strategies

Maintaining supply of drugs and minimizing wastes through proper stock management and disposal methods enhance rational use of drugs. The following are some of the strategies, but the best one that reduces dug waste is the FEFO system [80-86].

FIFO (First In First Out): Strategy implies that the products that were stocked first will move out first. Companies should use FIFO method if they are selling perishable goods. Companies selling products with relatively short demand cycles, such as clothes, also may have to pick FIFO to ensure they are not stuck with outdated styles in inventory.

LIFO (Last In First Out): In this warehouse management, the products which are brought in the last, moves out the first. LIFO is used in case of products which do not have a shelf life.

FEFO (First Expiry First Out): This term is used in logistics and inventory management to describe a way of dealing with product with a limited shelf life such as perishable products, or consumer goods with a specified expiry date. The product with the deadline for the next intake will be the first to be served or removed from stock. Majorly used in Pharmaceutical and Chemical industry where expired dates are calculated based on Batch expired date or Shelf life time.

The FEFO logic is a type of stock rotation that enable organizations to get a distribution process optimization, able to minimize the waste generation of finished and yet marketable products.

Reference manuals on drugs

Pharmacopoeias: the terms “pharmacopoeia” and “formulary” are used interchangeably. Both serve as current reference sources and provide an historical record of pharmacy practice, drug use, and drug availability. However, pharmacopoeia is far more complete than formulary.

α. ***Pharmacopeias***: Are authoritative treatises on drugs and preparations, their description, formulation, analytic composition, physical constants, main chemical properties used in identification, standards for strength, purity, and dosage, chemical tests for determining identity and purity, etc. They are usually published under governmental jurisdiction. The popular pharmacopeias are United States Pharmacopeia (USP) and British Pharmacopeia (BP) and European Pharmacopeia (EP). From Africa, only Egypt has ever prepared its own pharmacopeia. Thus, Ethiopia does not have its own pharmacopeia and uses either USP or BP for domestic production pharmaceuticals.

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β. **Formularies:** Are collections of formulas for the compounding of medicinal preparations. At its most basic level, a formulary is a list of medicines. Today, the main function of a prescription formulary is to specify particular medications that are approved to be prescribed at a particular hospital, in a particular health system, or under a particular health insurance policy. The development of prescription formularies is based on evaluations of efficacy, safety, and cost-effectiveness of drugs. Depending on the individual formulary, it may also contain additional clinical information, such as side effects, contraindications, and doses.

A national formulary contains a list of medicines that are approved for prescription throughout the country, indicating which products are interchangeable. It includes key information on the composition, description, selection, prescribing, dispensing and administration of medicines. Those drugs considered less suitable for prescribing are clearly identified. The popular formulary is the British National Formulary (BNF).

The procedures for developing national drug list/essential medicine list, standard treatment guidelines and formulary are all the same; together, they can be called the formulary process. STG are disease oriented, whereas formularies are drug oriented.

χ. **Standard Treatment Guideline (STG):** are systematically developed documents that help decisions about treatments for specific clinical conditions. They reflect a consensus on the treatments of first choice and alternative treatment for a range of medical conditions. STG are powerful tool in promoting rational drug use and standardization of prescribing patterns. It can be made for various levels of healthcare institutions (e.g. hospitals, health centers), regional states or nationally for a given country. The range of medicines included in STG should be limited to those on the NDL. Currently, the 5th edition-2020 is being finalized.

δ. **National Drug List (NDL):** it is essential drug list of a given country that satisfy the health care needs of the majority of the population; they should therefore be available at all times in adequate amounts and in appropriate dosage forms, at a price the community can afford. Currently the 6th edition, 2020 has been released [38,87].

Complementary and alternative medicine

Health care can broadly be divided into modern (conventional, western) and traditional (indigenous, complementary, alternative). One key difference between CAM and mainstream medicine is the strength of evidence supporting best practices. Mainstream medicine, when possible, bases its practices only on the most conclusive scientific evidence. In contrast, CAM bases its practices on evidence-informed practices—practices based on the best evidence available, even when such evidence does not meet the highest, strictest criteria for efficacy and safety.

Complementary and alternative medicine (CAM) or more appropriately Traditional, Complementary and alternative medicine (TCAM) is the term used for medical products and practices that are not part of standard medical care. It is an amorphous concept that comprises a range of long-standing and still evolving practices based on diverse beliefs and theories.

CAM is meant to treat the patient's mind, body, and spirit. Although not standardize, it can hardly be overlooked. Rather, it is recommended to implement integrative medicine.

Complementary, alternative, and integrative medicine is term often used interchangeably, but their meanings are different.

- *Complementary medicine*: Refers to non-mainstream practices used together with conventional medicine.
- *Alternative medicine*: Refers to non-mainstream practices used instead of conventional medicine.
- *Integrative medicine*: A total approach to medical care that combines standard medicine with the CAM practices that have been shown to be safe and effective. . It emphasizes a holistic, patient-focused approach to health care and wellness—often including mental, emotional, functional, spiritual, social, and community aspects—and treating the whole person rather than, for example, one organ system. It aims for well-coordinated care between different providers and institutions.

CAM therapies include Natural Products/dietary supplements (herbals/botanicals, vitamins and minerals, probiotics), mind and body practices (Massage, yoga, chiropractic and osteopathic manipulation, meditation, acupuncture, relaxation techniques, tai chi, hypnotherapy), and others (Ayurvedic medicine, traditional Chinese medicine, homeopathy, naturopathy). Although the safety of most CAM therapies has not been studied in clinical trials, many of these therapies have a good safety record. Many CAM therapies (e.g., nontoxic botanicals, mind-body techniques such as meditation and yoga, body-based practices such as massage) have been used for thousands of years with no evidence of harm, and many seem to have little potential for harm. However, still there are some safety considerations, which need further interventions. In Ethiopia, over 80% people rely on traditional medicines. The most

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common practices are herbal therapy, aroma therapy, bone settings and massage [88].

Part II: Pharmacology

Introduction to pharmacology

Pharmacology is derived from two Greek words; *pharmakon* that means 'drug' and logia that mean 'study. Pharmacology is thus shortly defined as "the study about drug". A drug is defined as any chemical substance that modifies biological system (increase, decrease, stabilize, damage etc) or kill infectious agents. More specifically, pharmacology is defined as the branch of pharmacy that studies the interactions between drugs and biological systems. Such interactions are explained by the *two major principles*; the pharmacokinetics (PK) and the pharmacodynamics (PD). PK studies the effects of biological systems (simply body) on the drugs. PK is shortly defined as "what the body does to the drug". It encompasses four processes, namely Absorption, Distribution, Metabolism and Excretion. PD studies the effects of the drugs on biological systems. PD is shortly defined as "what the drug does to the body". It encompasses both desirable (therapeutic effects) and undesirable effects (side effects, adverse effects, toxic effects) [42-45].

History

Rudolf Buchheim (1820–1879) was a German pharmacologist. He created the first pharmacological institute University of Dorpat at 1845. In 1867 he became professor of pharmacology and toxicology at the University of Giessen. Buchheim is remembered for his pioneer work in experimental pharmacology. He introduced the bioassay to pharmacology, and created a methodology for determining the quantitative and medical aspects of chemical substances [89].

A well-known student of his was chemist Oswald Schmiedeberg (1838–1921), who was to become the "founder of modern pharmacology".

Branches

Clinical pharmacology: The term 'clinical pharmacologist' was used in the professional sense to refer to those physicians who are specialists in clinical pharmacology. This notion must be a misunderstanding, since clinical pharmacologists deal with various aspects of drugs that require expert knowledge of drugs. It is known that pharmacists, but not physicians, are experts in drug therapy. Additionally, pharmacists were not considered as clinicians, and for the same wrong cause, pharmacists could not be clinical pharmacologists. Actually, the emergence of clinical pharmacy has made it clear that pharmacists are clinicians. Clinical pharmacologists involve in teaching, critical evaluation of drug therapies, drug utilization studies, pharmacoepidemiological and pharmacogenetics studies, Drug and Therapeutics Committees, drug information services, therapeutic drug monitoring, clinical drug toxicology assessment and monitoring, pharmacovigilance, antimicrobial drugs resistance containment, rational drug use, clinical trials and pharmacokinetics studies [90].

Toxicology: Study of harmful or toxic effects of drugs. Paracelsus (1493–1541) a Swiss physician, scientist, and philosopher is considered as the Father of Toxicology. He is known by his quote "*The dose makes the poison",* which means that only the dose identifies a poison from a therapeutic agent [91].

Pharmacogenetics and pharmacogenomics: Pharmacogenetics, the study of genetic influences on responses to drugs, initially focused on familial idiosyncratic drug reactions, where affected individuals show an abnormal – usually adverse – response to a class of drug. Rebranded as pharmacogenomics, it now covers broader genetically based variations in drug response, where the genetic basis is more complex, the aim being to use genetic information to guide the choice of drug therapy on an individual basis – so-called personalized medicine. The underlying principle is that differences between individuals in their response to therapeutic drugs can be predicted from their genetic make-up [53].

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Principles of pharmacology

Pharmacokinetics

Pharmacokinetics (PK) is the study of the way drug molecules behave in the body after administration (Figure 6). Four distinctive yet somewhat interrelated processes occur between the administration and the elimination of a drug from the body. These sequential events are called the ADME processes of the drug after administration, i.e., absorption, distribution, metabolism, and excretion [92].

Absorption

Absorption is the transfer of a drug from the site of administration to the bloodstream. The rate and extent of absorption depend on the environment where the drug is absorbed, chemical characteristics of the drug, and the route of administration. Routes of administration other than intravenous may result in partial absorption and lower bioavailability.

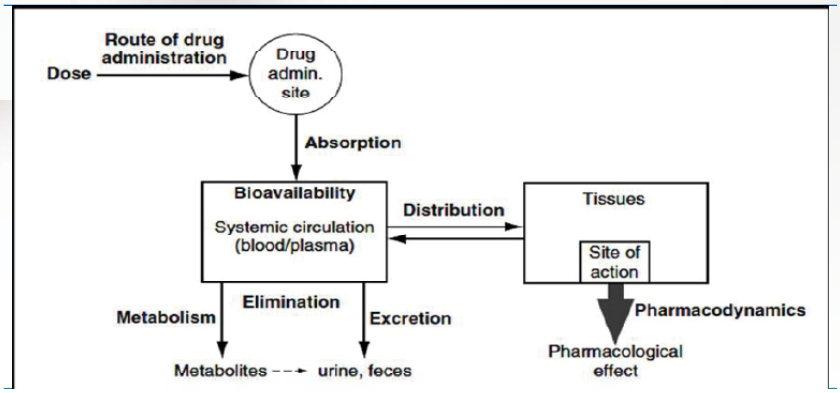

Figure 6: Drug-body interaction.
Legend: The drug-body interaction shown is about pharmacokinetics and pharmacodynamics. Pharmacokinetics is describes the movement of drugs through the body, whereas pharmacodynamics delas with the body's biological response to drugs uncluding side effects.

Absorption from GIT

Depending on their chemical properties, drugs may be absorbed from the G I tract by passive diffusion, facilitated diffusion, active transport, or endocytosis [42-45].

ι. Passive diffusion

Passive diffusion is a transport of drugs from an area of high concentration to one of lower concentration. It does not involve a carrier, is not saturable, and shows low structural specificity. The vast majority of drugs are absorbed by this mechanism. Water-soluble drugs penetrate the cell membrane through aqueous channels or pores, whereas lipid-soluble drugs readily move across most biologic membranes due to solubility in the membrane lipid bilayers.

ιι. Facilitated diffusion

Facilitated diffusion is a process where drugs enter the cell through specialized transmembrane carrier proteins that facilitate the passage of large molecules. These carrier proteins undergo conformational changes, allowing the passage of drugs or endogenous molecules into the interior of cells. It does not require energy, can be saturated, and may be inhibited by compounds that compete for the carrier.

ιιι. Active transport

This mode of drug entry also involves specific carrier proteins that span the membrane. However, active transport is energy dependent, driven by the hydrolysis of ATP. It is capable of moving drugs against a concentration gradient, from a region of low drug concentration to one of higher concentration. The process is saturable. Active transport systems are selective and may be competitively inhibited by other cotransported substances.

ιϖ. Endocytosis

This type of absorption is used to transport drugs of exceptionally large size across the cell membrane. Endocytosis involves engulfment of a drug by the cell membrane and transport into the cell by pinching off the drug-filled vesicle. Vitamin B_{12} is transported across the gut wall by endocytosis.

Factors influencing absorption

- **Physicochemical properties of drugs:** A given solid dosage form should be disintegrated and dissolved before absorbed from GIT. However, drugs already in liquid form do not need such changes. Thus, drugs physical properties such as solubility, particle size and dissolution affect absorption from GIT.

Additionally, chemical properties also affect absorption. Polar/water soluble and ionized (charged particles)

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drugs cannot be easily absorbed from GIT. They should be either small to pass through water pores, or need carrier transporters or energy (ATP) to traverse the membrane. Conversely, polar/lipid soluble and unionized/non-ionized drugs can easily cross lipid soluble GIT membranes by simple passive diffusion.

- **Effect of pH on drug absorption:** Most drugs are either weak acids or weak bases. A drug passes through membranes more readily if it is uncharged. Acidic drugs are uncharged in stomach (acidic) and charged in small intestine (basic/alkaline); whereas basic drugs are charged in stomach and uncharged in small intestine.

- **Blood flow to the absorption site:** The intestines receive much more blood flow than does the stomach, so absorption from the intestine is favored over the stomach.

- **Total surface area available for absorption:** With a surface rich in brush borders containing microvilli, the intestine has a surface area about 1000-fold that of the stomach. High surface favors more efficient absorption.

- **Contact time at the absorption surface:** Anything that hastens the transport of the drug through the GI tract (e.g., severe diarrhea) reduces the extent of absorption. Conversely, anything that delays the transport of the drug from the stomach to the intestine (e.g. food) delays the rate of absorption.

- **Expression of P-glycoprotein:** P-glycoprotein is a transmembrane transporter protein responsible for transporting various molecules, including drugs, across cell membranes. It "pumps" drugs out of cells. Thus, high expression reduces drug absorption and is also associated with multidrug resistance.

Bioavailability

Bioavailability is the rate and extent to which an administered drug reaches the systemic circulation. It is also defined as the fraction (F) of unchanged drug reaching the systemic circulation by any route. It is also called the area under the curve (AUC). Drugs with equal bioavailability are called bioequivalent drugs [61,62].

$$\text{Bioavailability } (F) = \frac{\text{AUC } (\text{route})}{\text{AUC } (\text{I.V.})} \text{ x } 100$$

A drug administered through IV achieves 100% bioavailability as it rapidly enters the circulation. With other routes, only part of the administered dose appears in the plasma. Thus, bioavailability for other routes is determined by comparing plasma levels of a drug after a particular route with levels achieved by IV routes. By plotting plasma concentrations of the drug versus time, the area under the curve (AUC) can be measured (Figure 7).

Factors that influence bioavailability

In contrast to IV administration, which confers 100% bioavailability, orally administered drugs often undergo first-pass metabolism. This biotransformation, in addition to chemical and physical characteristics of the drug, determines the rate and extent to which the agent reaches the systemic circulation.

First-pass hepatic metabolism: When a drug is absorbed from the G I tract, it enters the portal circulation before entering the systemic circulation. High metabolism in the liver or gut wall reduces the amount of unchanged drug entering the systemic circulation is decreased. This is referred to as first-pass metabolism. For example, more than 90% of *nitroglycerin* is cleared during first-pass metabolism. That is why it given through sublingual route. Drugs with high first-pass metabolism should be given through alternative routes or in doses sufficient to ensure that enough active drugs reaches the desired site of action.

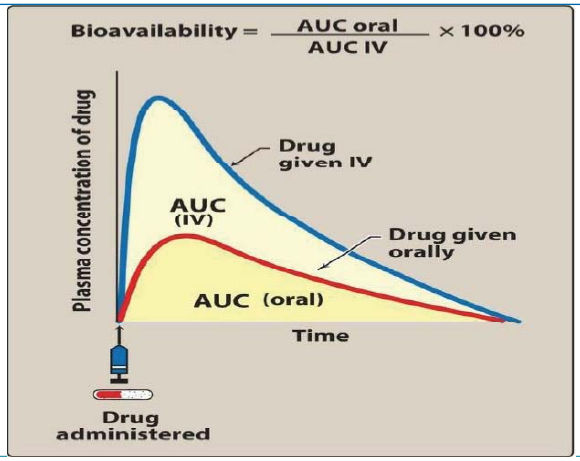

Figure 7: AUC for PO and IV administered drugs.
Legend: A drug given by the IV route will have an absolute bioavailability of 100% (f = 1), whereas drugs given by PO route usually has an absolute bioavailability of less than one.

Solubility of the drug: Very hydrophilic drugs are poorly absorbed because of the inability to cross lipid-rich cell membranes. Paradoxically, drugs that are extremely lipophilic are also poorly absorbed, because they are insoluble in aqueous body fluids and, therefore, cannot gain access to the surface of cells. For a drug to be readily absorbed, it must be largely lipophilic, yet have some solubility in aqueous solutions. This is one reason why many drugs are either weak

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acids or weak bases.

Chemical instability: Some drugs, such as *penicillin G*, are unstable in the pH of gastric contents. Others, such as *insulin*, are destroyed in the GI tract by degradative enzymes.

Nature of the drug formulation: Drug absorption may be altered by factors unrelated to the chemistry of the drug. For example, particle size, salt form, crystal polymorphism, enteric coatings, and the presence of excipients (such as binders and dispersing agents) can influence the ease of dissolution and, therefore, alter the rate of absorption.

Plasma concentration-time curve

For efficient pharmacotherapy, appropriate route of administration, dosage, and dosing interval must be chosen first. Selection of a regimen depends on various patient and drug factors, including how rapidly therapeutic levels of a drug must be achieved. Therapy may consist of a single dose of a drug. More commonly, drugs are continually administered, either as an IV infusion or in IV or oral fixed-dose/fixed-time interval regimens. Continuous or repeated administration results in accumulation of the drug until a steady state occurs. Steady-state concentration is reached when the rate of drug elimination is equal to the rate of drug administration, such that plasma and tissue levels remain relatively constant.

The goal of drug therapy is to achieve and maintain concentrations within a therapeutic response window while minimizing toxicity and/or adverse effects. With careful titration, most drugs can achieve this goal. If the therapeutic window of the drug is small, extra caution should be taken in selecting a dosage regimen, and drug levels should be monitored to ensure attainment of the therapeutic range. Drug regimens are administered as a maintenance dose and may require a loading dose if rapid effects are warranted. A "loading dose" of drug is administered to achieve the desired plasma level rapidly, followed by a maintenance dose to maintain the steady state

In general, the loading dose can be calculated as:

Loading dose = $(V_d) \times$ (desired steady-state plasma concentration)/F

Disadvantages of loading doses include increased risk of drug toxicity and a longer time for the plasma concentration to fall if excess levels occur.

Drugs are generally administered to maintain a C_{ss} (Figure 8) within the therapeutic window. It takes 4 to 5 half-lives for a drug to achieve C_{ss}. To achieve a given concentration, the rate of administration and the rate of elimination of the drug are important.

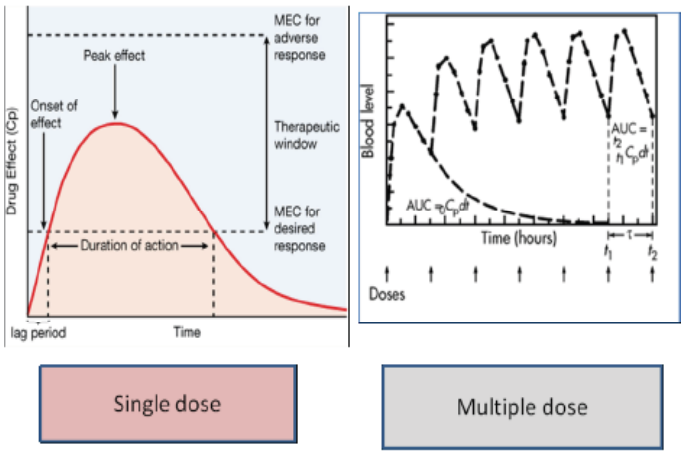

Figure 8: Steady state concentration for multiple doses.
Legend: Steady state is critical in selecting an appropriate dose and dosing frequency to achieve safe, therapeutic drug concentrations in patients. It describes a dynamic equilibrium in which drug concentrations consistently stay within therapeutic limits for long, potentially indefinite, periods.

Drug Distribution

Drug distribution is the process by which a drug reversibly leaves the bloodstream and enters the extracellular fluid and tissues. The parameter that describes the extent of drug distribution is called volume of distribution (Vd). Vd is not a physiological or physical volume, it is apparent and hypothetical volume. But, it can be useful to compare the distribution of a drug with the volumes of the water compartments in the body [42-45].

It is calculated by dividing the concentration that ultimately gets into the systemic circulation (Cp) by the plasma concentration at time zero (C_0).

$V_d = C_p/C_0$

This process can be most easily analyzed by plotting the log of the plasma drug concentration (C_p) versus time. The concentration of drug in the plasma can be extrapolated back to time zero (the time of IV bolus) on the Y axis to determine C_0, which is the concentration of drug that would have been achieved if the distribution phase had occurred instantly.

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The distribution of a drug from the plasma to the interstitium depends on blood flow, capillary permeability, tissue volume, degree of binding of the drug to plasma and tissue proteins, and relative lipophilicity of the drug.

Blood flow: The rate of blood flow to the tissue capillaries varies widely. For instance, blood flow to "vessel-rich organs" (brain, liver, and kidney) is greater than that to the skeletal muscles, adipose tissue, skin, and viscera.

Capillary permeability: In the liver and spleen, a significant portion of the basement membrane is exposed due to large, discontinuous capillaries through which large plasma proteins can pass. In the brain, the capillary structure is continuous, and there are no slit junctions. Polar drugs generally fail to enter the CNS because they cannot pass through the endothelial cells that have no slit junctions.

Binding of drugs to plasma and tissue proteins: Reversible binding to plasma proteins sequesters drugs in a non-diffusible form and slows transfer out of the vascular compartment. The higher the plasma binding, the lower the volume of distribution. This might lead to low desired effect. Albumin is the major drug-binding protein that mainly binds acidic drugs, but it also binds basic drugs. Alpha-glycoprotein is another drug-binding protein that selectively binds basic drugs.

Many drugs accumulate in tissues, leading to higher concentrations in tissues than in interstitial fluid and blood. The higher the tissue binding, the higher the volume of distribution. Tissue reservoirs may serve as a major source of the drug and prolong its actions or cause local drug toxicity.

Lipophilicity: Lipophilic drugs readily move across most biologic membranes. These drugs dissolve in the lipid membranes and penetrate the entire cell surface.

Body water compartments

Once a drug enters the body, it has the potential to distribute into any one of the three functionally distinct compartments of body water or to become sequestered in a cellular site.

- **Plasma compartment:** If a drug has a high molecular w eight or is extensively protein bound, it is too large to pass through the slit junctions of the capillaries and, thus, is effectively trapped within the plasma (vascular) compartment. As a result, it has a low V_d that approximates the plasma volume or about 4L in a 70-kg individual. *Heparin* shows this type of distribution.

- **Extracellular fluid:** If a drug has a low molecular weight but is hydrophilic, it can pass through the endothelial slit junctions of the capillaries into the interstitial fluid. However, hydrophilic drugs cannot move across the lipid membranes of cells to enter the intracellular fluid. Therefore, these drugs distribute into a volume that is the sum of the plasma volume and the interstitial fluid, which together constitute the extracellular fluid (about 20% of body w eight or 14L in a 70-kg individual). Aminoglycoside antibiotics show this type of distribution.

- **Total body water:** If a drug has a low molecular weight and has enough lipophilicity, it can move into the interstitium through the slit junctions and pass through the cell membranes into the intracellular fluid. These drugs distribute into a volume of about 60% of body weight or about 42L in a 70-kg individual.

In general, a larger V_d indicates greater distribution into tissues; a smaller V_d suggests confinement to plasma or extracellular fluid. If a drug has a large V_d, most of the drug is in the extraplasmic space and is unavailable to the excretory organs. Therefore, any factor that increases V_d can increase the half-life and extend the duration of action of the drug. An exceptionally large V_d indicates considerable sequestration of the drug in some tissues or compartments.

Elimination

Once a drug enters the body, the process of elimination begins. Elimination is an irreversible removal of drug from the body. It involves metabolism (biotransformation) and excretion. Together, these elimination processes decrease the plasma concentration exponentially.

I. **Metabolism:** The kidney cannot efficiently excrete lipophilic drugs that readily cross cell membranes and are reabsorbed in the distal convoluted tubules. Therefore, lipid-soluble agents are first metabolized into more polar (hydrophilic) substances in the liver via two general sets of reactions, called phase I and phase II (Figure 9).

Phase I

Phase I reactions convert lipophilic drugs into more polar molecules by introducing or unmasking a polar functional group, such as –OH or $–NH_2$. Phase I reactions usually involve reduction, oxidation, or hydrolysis. Phase I metabolism may increase, decrease, or have no effect on pharmacologic activity.

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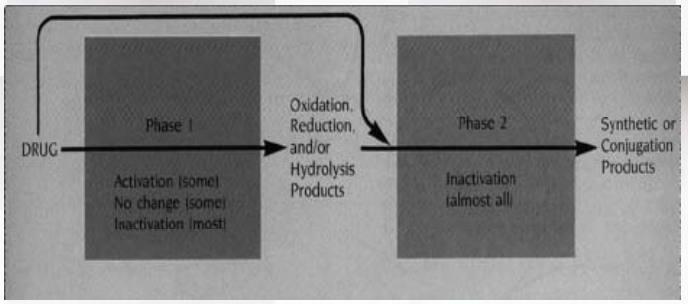

Figure 9: Phase I & Phase II metabolism.
Legend: Phase I metabolism converts a parent drug to polar active metabolites while phase II metabolism converts a parent drug to polar inactive metabolites. As depicted in the figure, some drugs can directly jump into Phase II metabolism.

The phase I reactions most frequently involved in drug metabolism are catalyzed by the cytochrome P450 (CYP) system. However, phase I metabolism is not exclusively mediated by CYP. There are other enzymes (e.g.monoamineoxidase-MAO,alcohol dehydrogenase, esterase,hydroxylase etc.) which take part in phase I metabolism.

CYP is a superfamily of heme-containing isozymes located in most cells, but primarily in the liver and GI tract. There are currently3 families for these enzymes: CYP1, CYP2, and CYP3. Each family has subfamilies: A, B, C, D, E, F. Each subfamily has in turn homolog genes represented by numbers. The family name is indicated by the Arabic number that follows CYP, and the capital letter designates the subfamily, for example, CYP3A. A second number indicates the specific isozyme, as in CYP3A4.

Because there are many different genes that encode multiple enzymes, there are many different P450 isoforms. These enzymes have the capacity to modify a large number of structurally diverse substrates. In addition, an individual drug may be a substrate for more than one isozyme. Seven isozymes (CYP3A 4/5, CYP2D6, CYP2C9, CYP2C19, CYP2B6, CYP2E1 and CYP1A2) are responsible for the vast majority of P450-catalyzed reactions. Among these, CYP3A4/5 alone is responsible for over 50% drugs metabolism, whereas CYP2D6 is responsible for a quarter of drugs in market. Considerable amounts of CYP3A4/5 are also found in intestinal mucosa, accounting for first-pass metabolism of some drugs. Phase I metabolism is non-saturable as there are excess amounts CYP enzymes. Any amount of drugs is metabolized [42-45,52-59].

Some of these isozymes, notably CYP2D6, CYP2C9 and CYP2C19, exhibit genetic variations/genetic polymorphism, which may alter the efficacy and safety of substrate drugs.

CYP2D6 exhibits genetic polymorphism. There are three variant genes of CYP2D6 isozymes that contribute to poor metabolizers, slow metabolizers and ultra-fast metabolizers; in addition to the wild/natural/original gene that contribute to fast metabolizers. For example, poor metabolizers obtain no benefit from the opioid analgesic codeine, because they lack the CYP2D6 enzyme that activates the drug to morphine. Conversely, ultra-fast metabolizers are at risk of medullary depression due to high accumulation of morphine. About 29% of Ethiopians are ultra-fast metabolizers. They are thus at high risk of morphine side effects if they take the normal dose of codeine designed for ultra-fast metabolizers. Similar polymorphisms have been characterized for the CYP2C9 and CYP2C19 isozymes. For instance, clopidogrel carries a warning that patients who are CYP2C19 "poor metabolizers" have a diminished antiplatelet effect when taking this drug and an alternative medication should be considered. Clopidogrel is a prodrug, and CYP2C19 activity is required to convert it to the active metabolite.

CYP inducers

The CYP450-dependent enzymes are an important target for pharmacokinetic drug interactions. Certain drugs are capable of inducing CYP isozymes. This results in increased biotransformation of drugs and can lead to significant decreases in plasma concentrations of drugs metabolized by these CYP isozymes, often with concurrent loss of pharmacologic effect. The important enzyme inducers are *phenobarbital*, *rifampin*, and *Carbamazepine.*

CYP inhibitors

Inhibition of drug metabolism can lead to significant increases in plasma drug concentration and resultant adverse effects or drug toxicity. The most common form of inhibition is through competition for the same isozyme. Some drugs, however, are capable of inhibiting reactions for which they are not substrates, leading to drug interactions. The more important CYP inhibitors are *erythromycin*, *ketoconazole*, and *ritonavir*, because they each inhibit several CYP isozymes.

Phase II

This phase consists of conjugation reactions. It is also called sysnthetic reaction. Drugs already possessing an –OH , –NH_2, or -COOH group may enter phase II directly and become conjugated without prior phase I metabolism.

Moreover, sufficiently polar metabolite from phase I can be directly excreted. However, many phase I metabolites are still too lipophilic to be excreted. A subsequent conjugation reaction with an endogenous substrate, such as glucuronic acid, glutathione, sulfuric acid, acetic acid etc. through mediation of the corresponding enzymes UDP-glucuronosyltransferase, glutathione-*S-transferase; sulfotransferase;N-acetyltransferase* results in polar, usually more water-soluble compounds. Glucuronidation is the most common and the most important conjugation reaction. Phase II metabolites (drug conjugates) are often therapeutically inactive. A notable exception is *morphine-6-glucuronide*, which is more potent than *morphine*. The highly polar drug conjugates are then excreted by the kidney or in bile.

Phase II also called synthetic or conjugation reaction. Phase II metabolism is saturable.

Acetaminophen which is also called paracetamol is metabolized by CYP3A4 and CYP2E1. Over 95% of phase I metabolites are conjugated by glucuronidation and sulfation into non-toxic substances. The alternative P450-dependent GSH conjugation pathway accounts for the remaining 5%. When paracetamol intake far exceeds therapeutic doses, the glucuronidation and sulfation pathways are saturated, and the phase I become increasingly important. Little or no hepatotoxicity results as long as hepatic GSH is available. In absence of adequate GSH a reactive, hepatotoxic metabolite called *N-acetylbenzoiminoquinone accumulates.* Thus, daily intake greater than 4g is not recommended. *N*-acetylcysteine is a chemical analog of GSH and thus can replete GSH and reverse the hepatoxicity.

Factors affecting drug metabolism

- Enzymes induction (Phenobarbitone, Rifampin)
- Enzyme inhibition (chloroquine, erythromycin)
- Genetics variations (INH: Slow/fast acetylators): *slow acetylator is associated with a higher incidence of peripheral neuritis.*
- Nutrition state: e.g. fasting vs. conjugates
- Overdose: e.g. paracetamol (hepatotoxicity)
- Age: e.g. chloramphenicol (gray baby syndrome)
- Sex: Diazepam (faster in females);propranolol (faster in males)
- Disease state: hepatic and renal
- Route of Administration: PO vs. IV

ii. Excretion: Drugs must be sufficiently polar to be eliminated from the body. Removal of drugs from the body occurs via a number of routes; the most important is elimination through the kidney into the urine. Patients with renal dysfunction may be unable to excrete drugs and are at risk for drug accumulation and adverse effects [42-45].

Renal elimination of a drug

A drug passes through several processes in the kidney before elimination: glomerular filtration, active tubular secretion, and passive tubular reabsorption.

Glomerular filtration

Drugs enter the kidney through renal arteries, which divide to form a glomerular capillary plexus. Free drug (not bound to albumin) flows through the capillary slits into the Bowman space as part of the glomerular filtrate. The glom erular filtration rate (GFR) is normally about 120mL/m in/1.73m ^{2} but may diminish significantly in renal disease. Lipid solubility and pH do not influence the passage of drugs into the glomerular filtrate. However, variations in GFR and protein binding of drugs do affect this process.

Proximal tubular secretion

Drugs that were not transferred into the glomerular filtrate leave the glomeruli through efferent arterioles, which divide to form a capillary plexus surrounding the nephric lumen in the proximal tubule. Secretion primarily occurs in the proximal tubules by two energy-requiring active transport systems: one for anions (for example, deprotonated forms of weak acids) and one for cations (for example, protonated forms of weak bases). Each of these transport systems shows low specificity and can transport many compounds. Thus, competition between drugs for these carriers can occur within each transport system.

Distal tubular reabsorption

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As a drug moves toward the distal convoluted tubule, its concentration increases and exceeds that of the perivascular space. The drug, if uncharged, may diffuse out of the nephric lumen, back into the systemic circulation. Manipulating the urine pH to increase the fraction of ionized drug in the lumen may be done to minimize the amount of back diffusion and increase the clearance of an undesirable drug. Generally, weak acids can be eliminated by alkalinization of the urine (e.g. by $NaHCO_3$), whereas elimination of weak bases may be increased by acidification (e.g. by NH_4Cl) of the urine. This process is called "ion trapping."

Elimination through other routes

Drug excretion may also occur via the intestines, bile, lungs, and breast milk, among others. Drugs that are not absorbed after oral administration or drugs that are secreted directly into the intestines or into bile are excreted in the feces. The lungs are primarily involved in the elimination of anesthetic gases. Elimination of drugs in breast milk may expose the breast-feeding infant to medications and/or metabolites being taken by the mother and is a potential source of undesirable side effects to the infant. Excretion of most drugs into sweat, saliva, tears, hair, and skin occurs only to a small extent. Total body clearance and drug half-life are important measures of drug clearance that are used to optimize drug therapy and minimize toxicity.

Clerance is the measure of the ability of the body to eliminate the drug.

Dosage adjustment

When a patient has an abnormality that alters the half-life of a drug, adjustment in dosage is required. Patients who may have an increase in drug half-life include those with 1) diminished renal or hepatic blood flow , for example, in cardiogenic shock, heart failure, or hemorrhage; 2) decreased ability to extract drug from plasma, for example, in renal disease; and 3) decreased metabolism, for example, when a concomitant drug inhibits metabolism or in hepatic insufficiency, as with cirrhosis. These patients may require a decrease in dosage or less frequent dosing intervals. In contrast, the half-life of a drug may be decreased by increased hepatic blood flow, decreased protein binding, or increased metabolism .This may necessitate higher doses or more frequent dosing intervals.

First order and Zero order kinetics

In first order kinetics, the rate of drug metabolism and elimination is directly proportional to the concentration of free drug. This means that a constant fraction of drug is metabolized per unit of time (that is, with each half-life, the concentration decreases by 50%). First-order kinetics is also referred to as linear kinetics.

In zero-order kinetics, the enzyme is saturated by a high free drug concentration, and the rate of metabolism remains constant over time. This means that a constant amount of drug is metabolized per unit of time. The rate of elimination is constant and does not depend on the drug concentration. Zero-order kinetics is also called nonlinear kinetics.

Pharmacodynamics

Pharmacodynamics describes the actions of a drug on the body. Most drugs (ligands) exert effects, both beneficial and harmful, by interacting with specialized target macromolecules, called receptors. A receptor is defined as any biologic molecule to which a drug binds and produces a measurable response. Although the term receptor specifically represents membrane-bound proteins that transduce extracellular signals into intracellular responses, generally it represents any drug target (e.g. enzymes, nucleic acids and structural proteins). Not all drugs exert effects by interacting with a receptor. Antacids, for instance, chemically neutralize excess gastric acid, thereby reducing stomach upset [93].

Cells have many different types of receptors, each of which are specific for a particular drug and produce a unique response. Cardiac cell membranes, for example, contain β-adrenergic receptors and muscarnic receptors. They bind and respond to norepinephrine and acetylcholine, respectively, and produce opposite effects. These two receptor populations dynamically interact to control the heart's vital functions. As a matter of specificity, β-adrenergic receptors do not bind acetylcholine and muscarnic receptors do not bind norepinephrine. However, it must be emphasized that no drug acts with complete specificity.

Drug-receptor reactions: Receptors exist in at least two states, inactive (R) and active (R*), that are in reversible equilibrium with one another, usually favoring the inactive state. Occupation of a receptor by a drug molecule may or may not result in *activation* of the receptor. By activation, we mean that the receptor is affected by the bound molecule in such a way as to alter the function of the cell and elicit a tissue response. Binding and activation represent two distinct steps in the generation of the receptor-mediated response by an agonist. If a drug binds to the receptor without causing activation and thereby prevents the agonist from binding, it is termed a *receptor antagonist* (Figure 10). The tendency of a drug to bind to the receptor, and once bound, to activate the receptor is denoted by its efficacy. Drugs of high

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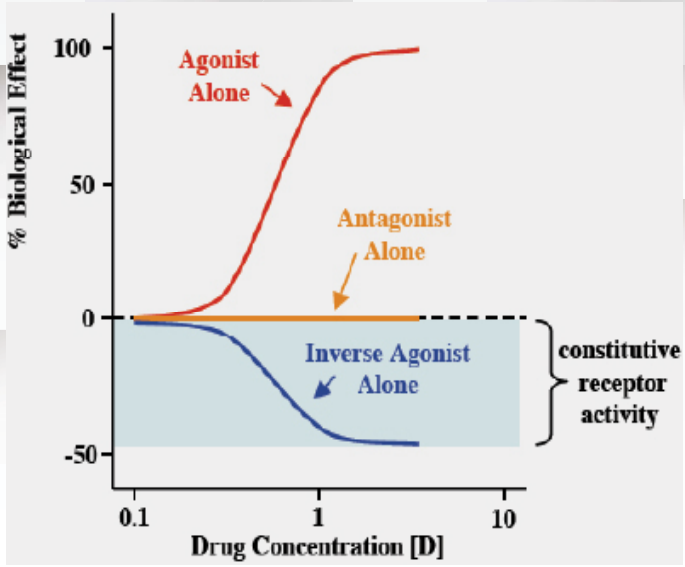

Figure 10: Showing agonist, antagonist and reverse agonis.
Legend: An agonist increases the activity of a receptor above its basal level, whereas an inverse agonist decreases the activity below the basal level. The efficacy of a full agonist is by definition 100%, a neutral antagonist has 0% efficacy, and an inverse agonist has < 0% (i.e., negative) efficacy.

potency generally have a high affinity for the receptors and thus occupy a significant proportion of the receptors even at low concentrations [93].

a) Full agonist: drug that binds to the receptor and causes the equilibrium to shift from R to R* to produce a biologic effect. Full agonists bind to a receptor, stabilizing the receptor in its active state and are said to have an intrinsic activity (ability to activate the receptor and cause a cellular response) of one. Full agonists produce maximum efficacy (E_{max}). E.g. Phenylephrine.

b) Partial agonists: shift the equilibrium from R to R*, but the fraction of R* is less than that caused by an agonist. Partial agonists have intrinsic activities greater than zero but less than one. Even when all the receptors are occupied, partial agonists cannot produce the same E_{max} as a full agonist. E.g. Pentazocine

c) Inverse agonists: stabilize the inactive R form and cause R* to convert to R. This decreases the number of activated receptors to below that observed in the absence of drug. Some receptors show a spontaneous conversion from R to R * in the absence of an agonist. Although we are accustomed to thinking that receptors (e.g benzodiazepines) are activated only when an agonist molecule is bound, there are cases where an appreciable level of activation (constitutive activation) may exist even when no ligand is present. Drugs that reduce the level of constitutive activation are called inverse agonists. Inverse agonists can be regarded as drugs with negative efficacy.

d) Antagonists: drugs that bind to the receptor but do not increase the fraction of R*, instead stabilizing the fraction of R. Antagonists bind to a receptor with high affinity but possess zero intrinsic activity. An antagonist has no effect on biological function in the absence of an agonist, but can decrease the effect of an agonist when present. Antagonism may occur either by blocking the drug's ability to bind to the receptor or by blocking its ability to activate the receptor.

Types of antagonism

Reversible competitive antagonism: In the presence of a competitive antagonist, the agonist occupancy (i.e. proportion of receptors to which the agonist is bound) at a given agonist concentration is reduced. However, raising the agonist concentration can restore the agonist occupancy and the tissue response. The antagonism is therefore said to be surmountable. Competitive antagonism is the most direct mechanism by which one drug can reduce the effect of another (or of an endogenous mediator).

Irreversible competitive antagonism: Irreversible competitive antagonism occurs when the antagonist binds to the same site on the receptor as the agonist but dissociates very slowly, or not at all, from the receptors, with the result that no change in the antagonist occupancy takes place when the agonist is applied. Irreversible competitive antagonism occurs with drugs that possess reactive groups that form covalent bonds with the receptor. Since increasing the agonist concentration fails to overcome the blocking effect, the anatgonism is said to be insurmountable. However, sometimes there is possibility of restoration due to the agonists binding to spare receptors.

Non-competitive antagonism (Allosteric Modulation): In addition to the agonist binding site to which competitive antagonists also bind, receptors possess many other (allosteric) binding sites through which drugs can influence receptor function in various ways.

A fundamental difference between surmountable and insurmountable antagonists is that surmountable antagonists reduce agonist potency (increase EC_{50}) and insurmountable reduce agonist efficacy (decrease E_{max}) [42-45].

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Functional antagonism (Physiological antagonism)

When two drugs produce opposite actions that tend to cancel each other, the antagonism is said to be functional anatagonim. For example, histamine acts on receptors of the parietal cells of the gastric mucosa to stimulate acid secretion, while omeprazole blocks this effect by inhibiting the proton pump; the two drugs can be said to act as functional antagonists.

Chemical antagonism

This occurs by ionic binding that makes the other drug unavailable for interactions with receptors. e.g. Protamine vs. Heparin

Major receptor families: The membrane-bound receptors may be divided into four families [45].

α. **Ion-channel linked (Ionotrophic) receptors:** The extracellular portion of ionotropic receptors contains the drug-binding site. This site regulates the opening of the pore through which ions can flow across cell membranes. The channel is usually closed until the receptor is activated by an agonist, which opens the channel for a few milliseconds. Depending on the ion conducted through these channels, these receptors mediate fast and diverse functions, including neurotransmission and muscle contraction. For example, stimulation of the nicotinic receptor by acetylcholine opens a channel that allows sodium influx and potassium outflux across the cell membranes of neurons or muscle cells. This change in ionic concentrations across the membrane generates an action potential in a neuron and contraction in skeletal and cardiac muscle. On the other hand, agonist stimulation of the A subtype of the γ-aminobutyric acid (GABA) receptor increases chloride influx, resulting in hyperpolarization of neurons and less chance of generating an action potential.

β. **Gprotein–coupled (metabotropic) receptors:** The extracellular portion of this receptor contains the ligand-binding site, and the intracellular portion interacts with a G protein. There are many kinds of G proteins (G_s, G_i, and G_q), but all types are composed of three (α, β and γ) protein subunits. The α-subunit binds guanosine triphosphate (GTP), and the β and γ subunits anchor the G protein in the cell membrane. These subunits further interact with specific cellular effectors, usually an enzyme or an ion channel. The responses mediated by metabotropic receptors usually last several seconds to minutes. Often, the activated effectors produce "second messenger" molecules that further activate other effectors in the cell, causing a signal cascade effect. A common effector, activated by G_s and inhibited by G_i, is adenylyl cyclase, which produces the second messenger cyclic adenosine monophosphate (cAM P). The effector phospholipase C, when activated by G_q, generates two second messengers: inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG). DAG and cAMP activate specific protein kinases within the cell, leading to a myriad of physiological effects. IP_3 increases intracellular calcium concentration, which in turn activates other protein kinases.

χ. **Enzyme-linked(Kinase-linked) receptors:** This family of receptors undergoes conformational changes when activated by a ligand, resulting in increased intracellular enzyme activity. This response lasts for minutes to hours. The most common enzyme-linked receptors (for example, growth factors and insulin) possess tyrosine kinase activity. When activated, the receptor phosphorylates tyrosine residues on itself and other specific proteins. Phosphorylation can substantially modify the structure of the target protein, thereby acting as a molecular switch. For example, the phosphorylated insulin receptor inturn phosphorylates other proteins that now become active. Thus, enzyme-linked receptors often cause a signal cascade effect like that caused by G protein–coupled receptors.

δ. **Intracellular receptors:** The fourth family of receptors differs considerably from the other three in that the receptor is entirely intracellular, and, therefore, the ligand (for example, steroid hormones) must have sufficient lipid solubility to diffuse into the cell to interact with the receptor. The primary targets of activated intracellular receptors are transcription factors in the cell nucleus that regulate gene expression. The activation or inactivation of transcription factors alters the transcription of DNA into RNA and subsequently translation of RNA into proteins. The effect of drugs or endogenous ligands that activate intracellular receptors takes hours to days to occur. Other targets of intracellular ligands are structural proteins, enzymes, RNA, and ribosomes. For example, tubulin is the target of antineoplastic agents such as *paclitaxel*, the enzyme dihydrofolate reductase is the target of antimicrobials such as *trimethoprim*, and the 50S subunit of the bacterial ribosome is the target of macrolide antibiotics such as *erythromycin*.

Signal transduction: Drugs exert their effects, both beneficial and harmful, by interacting with receptors present on the cell surface or within the cell. Receptors transduce their recognition of a bound drug by initiating a series of reactions that ultimately result in a specific intracellular response. The drug–receptor complex initiates alterations in biochemical and/or molecular activity of a cell by a process called signal transduction [42-45].

Signal transduction has two important features: 1) the ability to amplify small signals and 2) mechanisms to protect the cell from excessive stimulation.

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Signal amplification

A characteristic of G protein–linked and enzyme-linked receptors is the ability to amplify signal intensity and duration via the signal cascade effect. Additionally, activated G proteins persist for a longer duration than does the original agonist–receptor complex. Further prolongation and amplification of the initial signal are mediated by the interaction between G proteins and their respective intracellular targets. Because of this amplification, only a fraction of the total receptors for a specific ligand may need to be occupied to elicit a maximal response.

Desensitization/Tachyphylaxis/Tolerance/Refractoriness/Resistance

Repeated or prolonged exposure of receptors to agonists or antagonists often causes receptor desensitization that result in diminished effects. This phenomenon, called tachyphylaxis, is often due to much stimulation that renders receptors unresponsive to the agonist. Desensitization and tachyphylaxis are synonymous terms used to describe this phenomenon, which often develops in the course of a few minutes. The term tolerance is conventionally used to describe a more gradual decrease in responsiveness to a drug, taking hours, days or weeks to develop, but the distinction is not a sharp one. The term refractoriness is also sometimes used, mainly in relation to a loss of therapeutic efficacy. Some receptors, particularly ion channels, require a finite time following stimulation before they can be activated again. During this recovery phase, unresponsive receptors are said to be "refractory." Drug resistance is a term used to describe the loss of effectiveness of antimicrobial or antitumor drugs.

Various mechanisms involve in the process of diminished receptors response to a given drug. One is a gradual decrease in the number of receptors expressed on the cell surface, as a result of internalization of the receptors (e.g. β-adrenoceptors) making them unavailable for further agonist interaction. This is also called down-regulation. Repeated exposure of a receptor to an antagonist, on the other hand, results in up-regulation of receptors, in which receptor reserves are inserted into the membrane, increasing the number of receptors available. Up-regulation of receptors can make cells more sensitive to agonists and/or more resistant to effects of the antagonist.

In some cases, desensitization is associated with depletion of an essential intermediate substance. Drugs such as amphetamine, which acts by releasing amines from nerve terminals, show marked tachyphylaxis because the amine stores become depleted. Reduced response to some drugs (e.g. barbiturates) occurs partly because repeated administration of the same dose produces a progressively lower plasma concentration, as a result of increased metabolic degradation. However, for nitrovasodilators reduced response occurs mainly from decreased metabolism, which reduces the release of the active mediator, nitric oxide. Diminution of a drug's effect may still occur when it is nullified by a homeostatic response. For example, the blood pressure-lowering effect of thiazide diuretics is limited because of a gradual activation of the renin–angiotensin system. Finally, some kind of physiological adaptation may occur as a result of altered gene expression.

Dose response relationship: The magnitude of the drug effect depends on receptor sensitivity to the drug and the drug concentration at the receptor site, which, in turn, is determined by both the dose of drug administered and by the drug's pharmacokinetic profile, such as rate of absorption, distribution, metabolism, and elimination. There are two types of dose-response relationships [42-45].

Graded dose–response relationship

As the concentration of a drug increases, its pharmacologic effect also gradually increases until all the receptors are occupied (the maximum effect). Plotting the magnitude of response against increasing doses of a drug produces a graded dose–response curve. Two important drug characteristics, potency and efficacy (Figure 11), can be determined by graded dose–response curves.

Potency: Potency is a measure of the amount of drug necessary to produce an effect. The concentration of drug producing 50% of the maximum effect (EC50) is often used to determine potency. A lesser amount of more potent drug is needed to obtain 50% effect compared to less potent one. Formulations of drugs reflect their potency.

Efficacy: Efficacy is the magnitude of response a drug

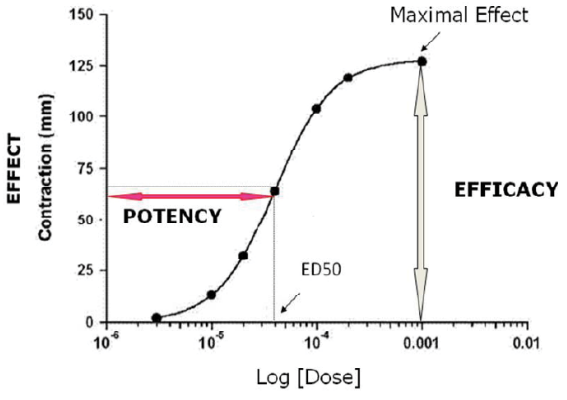

Figure 11: A sigmoid dose-response curve showing potency and efficacy. Legend: 'Potency' refers to the location of curve along the dose axis; 'efficacy' refers to the greatest attainable response of the system under measurement; 'slope' is the change in response per unit dose.

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causes when it interacts with a receptor. It is dependent on the number of drug–receptor complexes formed and the intrinsic activity. Maximal efficacy of a drug (Emax) assumes that the drug occupies all receptors, and no increase in response is observed in response to higher concentrations of drug. Efficacy is a more clinically useful characteristic than potency, since a drug with greater efficacy is more therapeutically beneficial than one that is more potent.

Quantal dose–response relationships

Quantal dose–response relationship describes the relationship between the dose of the drug and the proportion of a population that responds to it. Quantal dose– response curves are useful for determining doses to which most of the population responds A predetermined level of the response is designated as the point at which a response occurs or not. For any individual, the effect is categorized as either "occurs" or "does not occur". Quantal response is an "all or none" response. For example, a quantal dose–response relationship can be determined in a population for the antihypertensive drug atenolol. A positive response is defined as a fall of at least 5mmHg in diastolic blood pressure. A negative response is taken if the fall is below 5mmHg.

Adverse effects/Side effects

a. Adverse drug reaction: An adverse drug reaction is a general term referring to any untoward reaction to a medication. It may be termed a "side effect", when judged to be secondary to a main or therapeutic effect, and may result from an unsuitable or incorrect dosage or procedure, which could be due to medical error. Adverse effects may cause medical complications of a disease or procedure and negatively affect its prognosis. They may also lead to non-adherence with a treatment regimen. Common examples include diarrhea, nausea, teratogenicity, hypersensitivity and sedation.

Adverse drug reactions may be broadly divided into two types, type A and type B [45].

Type A reactions (Predictable): Type A reactions make up 85 to 90 percent of all adverse drug reactions. These can affect any individual, given sufficient dose and exposure, and are predictable from the known pharmacologic properties of a drug. Examples of type A reactions include diarrhea in response to antibiotics, gastritis in association with long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs), or aminoglycoside nephrotoxicity.

Type B reactions (Non-predictable): Type B reactions represent hypersensitivity reactions. It is sometimes called idiosyncratic reactions. They make up 10 to 15 percent of adverse drug reactions, occur in a susceptible subgroup of patients, and have signs and symptoms that are different from the pharmacologic actions of the drug. The great majority of hypersensitivity reactions are mediated by immunologic and/or inflammatory mechanism.

Drugs and pregnancy

The effects of drugs on the developing human are many and variable. By altering the time and the rate of cellular development, a medication may produce long term effects that are not demonstrable to the observer. The resulting effects might be spontaneous abortion, fetal loss, embryo-fetal morphological abnormalities, intrauterine growth restriction, and functional disabilities, such as intellectual disability [94,95].

The time of ingestion of a drug is critical in assessing the resultant effects on the fetus. The first two weeks (the 'all-or-nothing' phase) can result either in spontaneous abortion or in a normal embryo-fetal development. The period from the 3rd - 8th week of gestation is a period in which most of the morphological structures develop; it can lead to considerable phenotypical changes in the embryo, such as alterations in the central nervous system, limbs and face. From the 9th week of gestation some organs are still developing, like external genitalia and brain, and exposure to teratogens can culminate in functional abnormalities. However, most morphological characteristics are preserved from this phase onward.

Additionally, teratogenic effect of a particular drug may be specific to the species. The rabbit, for example, is highly susceptible to thalidomide as a teratogen, whereas the rat is relatively resistant to this drug. Hence, drug teratogenicity in animals cannot be uncritically extrapolated to humans. In addition, gestational age, drug dose, duration of administration, maternal-fetal blood pH gradient, differences in protein binding, variations in absorption and transplacental transfer, placental metabolism, and environmental factors must be considered.

Historically thalidomide is one of the most famous and notorious teratogens. This agent was used widely in Europe in 1959, after which an estimated 7000 infants were born with meromelia. The characteristic features of this syndrome include limb abnormalities that span from absence of the limbs to rudimentary limbs to abnormally shortened limbs, leading to its ban in most countries since 1961. As a result, the FDA created a risk classification for these substances during an international symposium of the Teratology Society in 1992. The level of risk of a given drug to the fetus is

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indicated by letters (A, B, C, D, F, N) [42-45].

The pregnancy letter designations were classified based on what was known from human and animal data. The limitation of letter categorization is that these letter categories are overly simplistic, and does not effectively communicate the risk a drug may have during pregnancy and lactation. Heavy reliance upon pregnancy categories often led to misinterpretation of the information, making prescribing decisions based on the pregnancy category rather than an understanding of the underlying information that informed the assignment of the pregnancy category.

Pregnancy and Lactation Labeling Rule (PLLR)

Since letter categories (A, B, C, D, and X) led to misinterpretation and errors in prescribing decisions, the FDA published a new rule, the "Pregnancy and Lactation Labeling Rule" (PLLR), for classification based on a narrative structure rather than a category system, which provides a clearer description of potential risks of drug exposure during pregnancy [94] Tables 1,2.

Table 1: Pharmacy abbreviations and acronyms.

Abbreviation	From the Latin	Meaning
No.	*Numero*	number
Rx	*recipere*	prescription
u.d	*ut dictum*	as directed
e.m.p	*ex modo prescripto*	as directed
q.s.	*quantum sufficiat*	a sufficient quantity
gtt(s)	gutta(e)	drop(s)
Tbsp		Tablespoon
Tsp		Teaspoon
Mitte	Mitte	Send
Nebul	Nebula	a spray
pulv.	Pulvis	Powder
rep., rept.	Repetatur	Repeats
Sig	Signa	write (directions on label)
A.s/a.l	*auris sinistra/aurio laeva*	left ear
a.u	*auris utrae*	both ears
o.d	*oculus dexter*	right eye
o.s	*oculus sinister*	left eye
o.u	*oculus uterque*	both eyes
p.o	*per os*	by mouth; orally
p.r	*per rectum*	Rectally
p.v	*per vaginam*	Vaginally
Stat	statim	Immediately
p.r.n	*pro re nata*	as needed (for)
h.s	hora somni	at bedtime
q.n	*quaque nocte*	every night
q.d	*quaque die*	once a day
b.i.d	bis in die	two times a day
t.i.d/t.d.s	ter in die/ ter die sumendum	three times a day
q.i.d	*quater in die*	four times a day
NS		Normal saline (0.9 % sodium chloride)
RL/LR		lactated Ringer's
D5LR		Dextrose 5 % in lactated Ringer's
D5NS		Dextrose 5 % in normal saline (0.9 % sodium chloride)
D5W		Dextrose 5 % in water
Supp	suppositorium	Suppository
Tab	tabella	Tablet
cap. caps.	capsula	Capsule
ung.	unguentum	Ointment

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Table 2: FDA letter based pregnancy category.	
Category	**Description**
A	**No risk in controlled human studies:** Adequate and well-controlled human studies have failed to demonstrate a risk to the fetus.
B	**No risk in other studies:** Animal studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women OR Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus.
C	**Risk not ruled out:** Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans.
D	**Positive evidence of risk:** There is positive evidence of human fetal risk, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
X	**Contraindicated in pregnancy:** Studies in animals or humans have demonstrated fetal abnormalities, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.
N	FDA has not yet classified the drug into a specified pregnancy category**.**

The rule requires the following two subsections:

I) Pregnancy: Information about use of the drug in pregnant women, which includes the dosing and potential risks to the developing fetus; information about registries of pregnant women affected by a drug or biological product, and a recommendation of inclusion in the drug label of the existence of any pregnancy registries;

II) Lactation: Information about using the drug while breastfeeding, which includes the amount of drug in breast milk and possible effects on the baby

PLLR provides the prescriber with

- Relevant information for critical decision-making when treating pregnant or lactating women
- More complete statement of the known risks based on the available data
- Considerations of medical/disease factors
- Animal data put in context of human exposure
- Human data added when available
- Explicitly states when no data are available

From June 30, 2015, these labeling changes came into effect in USA, to which prescription of drugs and biological products have to comply. In Ethiopia, leave alone the PLLR, even the FDA categorization rule is not effectively implemented.

Drug hypersensitivity reactions include exaggerated pharmacologic reactions to medications that result from an enhanced immunologic or inflammatory response [96].

Type I reactions these plasma cells produce IgE antibodies. Many of these reactions are caused by antibiotics of the β-lactam family (e.g. penicillin and its derivatives) that can lead to symptoms ranging from mild skin reaction to the life threatening anaphylactic shock. In the case of penicillin, the antibiotic binds covalently to high-molecular weight proteins such as albumin thus forming a molecule complex that can be recognized by IgE antibodies. During sensitization, these IgE antibodies bind to mast cells in tissues and basophiles in the blood via the FcεRI receptor. Subsequent cross-linking of the IgE antibody with the antigen elicits the type I reaction resulting in the release of histamines, leukotrienes and serotonin as well as prostaglandin causing allergic symptoms . Type I reactions are immediate reactions that take place directly after administration of the drug or up to 2 hours later. Typically, clinical manifestations contain symptoms such as urticaria, mild skin rashes and anaphylactic shock.

In non-immediate type II and type III reactions symptoms emerge 5 to 21 days after administration of the drug, however, first symptoms are usually observed after 24 to 48 hours. Both types are primarily IgG-mediated. Damage mediated by tissue-specific IgG or IgM antibodies is the basis for type II reactions: On exposure, the drug forms a hapten with a self-protein thus creating a modified self-protein. Binding of IgG or IgM to the modified self-tissue is followed by activation of normal immunoglobulin ejectors.

Drug specific type II reactions are mostly associated with the destruction of red blood cells and platelets, where the respective drug bound to the cell surface serves as an antigenic target for IgG antibodies leading to antibody-dependent cell-mediated cytotoxicity (ADCC).

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Consequently, the cell bound antibody then triggers clearance of the cell from the circulation by macrophages or NK cells that recognize the Fc part of the IgGantibodies *via* the FcγRIII (CD16) surface receptor. Examples are hemolytic anemia as an adverse reaction to methyldopa or leukopenia in the case of aminopyrine.

Type III hypersensitivity reactions are caused by soluble drug-haptens that form immune complexes with IgG antibodies. Larger aggregates are fixed by complement und consecutively cleared by phagocytes, however, smaller immune complexes deposit at local tissue sites where FcR binding on leukocytes and mast cells induces an inflammatory response leading to increased vascular permeability. Conditions that arise from type III reactions are serum sickness (especially β-lactams), drug-induced lupus erythematosus and thrombocytopenia (quinidine) or vasculitis or even DRESS (minocycline).

Type IV reactions take the longest time to develop, ranging from 2 days up to 20 days until first symptoms emerge. Symptoms include mild conditions such as MPE to more severe conditions such as TEN or SJS. Type IV ADRs are T-cell mediated drug hypersensitivity reactions based on the erroneous T-cell activation through HLA molecules on the surface of endogenous cells.

Drug safety indicators

Therapeutic index: The therapeutic index (TI) of a drug is the ratio of the dose that produces toxicity in half the population (TD_{50}) to the dose that produces a clinically desired or effective response (ED_{50}) in half the population:

$$TI = \frac{TD_{50}}{ED_{50}}$$

The TI is a measure of a drug's safety, because a larger value indicates a wide margin between doses that are effective and doses that are toxic. In agents with a low TI, dose is critically important and bioavailability critically alters the therapeutic effects. For drugs with large TI, bioavailability does not critically alter the therapeutic or clinical effects.

Obviously, it can only be measured in animals, and it is not a perfect guide to the safety of a drug in clinical use for several reasons:

- LD50 does not reflect the incidence of adverse effects in the therapeutic setting.
- ED50 depends on what measure of effectiveness is used. For example, the ED50 for aspirin used for a mild headache is much lower than for aspirin as an antirheumatic drug.

Both efficacy and toxicity are subject to individual variation. Individual differences in the effective dose or the toxic dose of a drug make it inherently less predictable, and therefore less safe, although this is not reflected in the therapeutic index [97].

Toxicology

Introduction: The word toxicology came from two Greek words; *toxicon* for poison and logia which mean *scientific study.* Great turning point came through Theophrastus Bombastus von Hohenheim (1493-1541) known as Paracelsus: "dosis sola facit venenum" ("the dose alone makes a thing poisonous"). Paracelsus is considered as a Father of Toxicology.

Toxicology is essentially a study of poisons and is concerned with:

- The chemical nature of poisons
- The interaction of poisons with biological systems
- Safety evaluation or toxicity testing of potentially toxic materials(substances)

A poison/toxin can be defined as any agent capable of producing a deleterious response in a biological system that seriously impairs function or produces death.

Toxicology was coined as modern science in the 17th century. In the 18th century, toxicology developed in the context of chemistry as a pure science and in the context of pharmacy as an applied science. The development of pharmacology was one of the main reasons for an expansion in toxicology at university level in the second half of the 19th century [91].

Branches of toxicology

The following are some of the major branches of Toxicology

Descriptive toxicology: Toxicity tests to obtain information that can be used to evaluate the risk that exposure to a

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chemical poses to humans and to the environment.

Regulatory toxicology: Judges whether a drug or other chemical has a low enough risk to justify making it available for its intended purpose.

Forensic toxicology: Combines analytical chemistry and fundamental toxicology. It is involved in postmortem investigations to establish the cause or circumstances of death.

Clinical toxicology: Focuses on diseases that are caused by or are uniquely associated with toxic substances.

Routes and sites of exposure

The routes and sites of exposure of toxicants can be:

- Ingestion (Gastrointestinal Tract)
- Inhalation (Lungs)
- Dermal/Topical (Skin)
- Injection
- Intravenous, intramuscular, Intraperitoneal
- Typical Effectiveness of Route of Exposure is as follows

  IV > inhalation > IP > IM > Ingestion > topical

Toxicity tests classification based on duration

Toxicity classification based on duration is indicated in the Table 3 below:

Prevention and management of poisoning: Many acute poisonings from drugs could be prevented. For clinical purposes, all toxic agents can be divided into two classes: those for which a specific treatment or antidote exists and those for which there is no specific treatment.

Table 3: Showing time of duration based classification of toxicity

Type	Duration	Frequency
Acute	< 24 hrs	Usually 1
Sub Acute	1 Month	Repeated
Sub Chronic	1-3 Months	Repeated
Chronic	>3 Months	Repeated

For the vast majority of drugs and other chemicals, there is no specific treatment; symptomatic medical care that supports vital functions is the only strategy. Generally, supportive therapy is the mainstay of the treatment of drug poisoning. The adage, "treat the patient, not the poison," remains the most basic and important principle of clinical toxicology [91].

Prevention of further absorption of poison

Prevention of further absorption of a given poison is possible through:

- Emesis
- Gastric Lavage
- Chemical Adsorption
- Purgatives

Enhanced elimination of the poison

Enhanced elimination is another strategy of preventing damage due to poisons. This is possible through:

- *Biotransformation*
- *Urinary excretion*
- *Dialysis*

Neutralization of the poison

Neutralization of the poison is possible through application of specific antidotes. Sometimes, a given antidote can

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neutralize more than a single chemical responsible for poisoning, in which case it is called universal antidote. This is simply a relative term, in comparison to those antidotes neutralizing a single toxicant alone. Nevertheless, there is no universal antidote in absolute term.

Generally, drugs used in toxicity management in Ethiopia are described in Table 4 [25].

Table 4: Antidotes and other substances used in toxicity management.

1	Acetylcysteine: 200mg/ml in 10ml ampoule	Paracetamol toxicity
2	Activated Charcoal 15gm/120ml, 25gm	Universal
3	Calcium Gluconate 10% in 10ml ampoule	Hyperkalemia management
4	Deferoxamine Mesylate 500mg in vial	Iron toxicity
5	Digoxin Immune (Fab Ovine) Digoxin-specific, antibody fragments 40mg	Digoxin toxicity
6	Flumazenil 0.5 mg/5 mL in ampoule	Benzodiazepine toxicity
8	Phytomenadione (Vitamin K1) 1mg/0.5ml, 10mg/ml in 1ml ampoule, Tablet, 10mg	Warfarin toxicity
9	Sodium Nitrite 3% (30mg/ml)	
10	Physostigmine 1mg/ml	Anticholinergic toxicity
11	Naloxone hydrochloride 0.4mg in 1ml ampule	Opioid toxicity
12	Pralidoxime Chloride 1000mg/vial, Tablet: 500mg	Cholinesterase inhibitors toxicity
13	Protamine sulphate 10mg/ml;	Heparin toxicity
14	Snake Venom Antiserum Polyvalent 10ml	Venoms

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Concluding remarks

Pharmacy is as old as human life, but pharmacology is not. Pharmacy is a practice discipline with clearly indicated code of practice; pharmacology is a science that improves pharmacy and pharmacotherapy. Pharmacotherapy is a clinical extension of pharmacology that is responsible for evolution of clinical pharmacy. The case of Ethiopia is different. In Ethiopia pharmacology is more respected than pharmacy. The reason for this is that health professionals besides pharmacy know pharmacy due to pharmacology alone. They had no chance of knowing pharmacy as different from pharmacology and broader, due to two reasons. First, they had no chance of learning other sub-disciplines (pharmaceutics, pharmaceutical chemistry, Pharmacognosy, pharmacoepidemiology etc.) of pharmacy except pharmacology. Second and most important, pharmacy profession is locked up in dispensary rooms and behind the counters; thus no chance of interacting in health care setups. So, it was pharmacology that bond pharmacy to other health disciplines until the evolution of clinical pharmacy. Today, the beginning of clinical pharmacy services has somehow brought pharmacy back to wards.

Pharmacy and medicine co-existed for centuries as integrated medical science. The physician diagnoses the disease and the apothecary prepares medicine. This had continued until 18th century, where they separated at Arab countries (including Egypt). The separation followed in the European countries and Canada and finally got shape in USA. The same history was not clearly stated in Africa and Ethiopia. In Ethiopia, pharmacy education and practice had begun by foreign based professionals. It was not known whether pharmacy and medicine co-existed or not. With the start of clinical pharmacy education and services, pharmacy and medicine have come closer, if not like the ancient times. Still many challenges are ahead with pharmacy from pharmacists (misapprehending the ever rapid changes in the field), policy makers and professional counterparts. However, one thing is sure; pharmacy will not give up in wards!

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