UNIT-III

Application of computers in pharmacy

DRUG INFORMATION AND STORAGE RETRIEVAL

The efficient use of drug information (DI) is an important skill for all pharmacists to have regardless of their practice site. In all pharmacy settings, pharmacists are recognized as drug experts and as providers of DI. It is imperative, therefore, that pharmacists know how to provide accurate and complete responses to DI requests. Keeping current with DI resources is challenging for the clinician because of the vast amount and the variable quality of available resources. Technology has also brought DI to the patient's bedside. Pharmacists should know what DI resources are available and be able to use these sources effectively and efficiently. Primary literature is the most up-to-date resource available to the clinician and consists of journal articles reporting original research, new ideas, or opinions. These resources are useful for research, education, and current awareness. Not all articles found in journals are considered primary literature; for example, review articles that summarize the literature are classified as tertiary resources. Secondary resources include indexing and abstracting systems that organize and provide easy retrieval of primary resources. Indexing systems include the article citation, with or without access to the abstract; some include a link to the full-text article. Abstracting systems provide not only the citation but also the abstract and often a link to the full-text article. Examples of secondary resources include MEDLINE (through PubMed, EBSCO, Ovid), Academic Search Premier, Cochrane Database of Systematic Reviews, Iowa Drug Information Service (IDIS), International Pharmaceutical Abstracts (IPA), Embase/Excerpta Medica, Biosis Previews/Biological Abstracts, CancerLit, SedBase, Reactions, Clin-Alert, Current Contents, and Toxline. Proper training is required for efficient use of these resources. Tertiary resources are sources that condense and summarize data from the primary literature. These include not only textbooks and compendia but also electronic databases (e.g., Micromedex, Lexicomp) and review articles. The best tertiary resources are written by experts in the field and are peer reviewed. If the tertiary resource is not current or comprehensive, a secondary resource should be consulted to locate primary literature on the topic. However, some questions can only be answered by using tertiary sources.

Internet sources of DI:

There has been an explosion of information available on the Internet for both the health care professional and the consumer. An estimated 60 million U.S. adults use search engines daily basis to explore more than 1 trillion Web pages; studies suggest that about 60% of adults search for health-related information. According to some top Internet researchers, the public is unable to find the information they seek almost 50% of the time. The quality of the information that they do find is a separate concern. Patients rely on the Internet for health and DI when they may not have access to a knowledgeable health care professional (HCP). Studies have shown that the younger population will use the Internet as one of their primary sources of DI. Older adults (60 years and older) prefer to talk to an HCP as their primary source of DI, but these patients will also access the Internet. Compared with an HCP, members of the public may have fewer skills to evaluate the validity of the DI that they receive from the Internet. The National Library of Medicine (NLM) has created a 16-minute video intended to help consumers distinguish a good Internet source of information (*www.nih.gov/MEDLINEplus/webevalu.html*). As the video points out, anyone can create an Internet site, and it is essential to determine the creator of the site, the creator's credibility, and the way to contact the organization who has ownership of the site. As with

any Internet source, pharmacists should evaluate the credibility, validity and reliability of the information. Health care professionals can rely on the same NLM concepts provided for consumers when searching the Internet. Many Internet services, either available free or for a paid subscription, can be invaluable sources of high-quality, evidence-based medicine. Many sites provide HCPs with fast results to DI questions and even access to professional journals. The skill of the researcher is essential in getting to the best information, and studies have documented that skill level can make a difference in the quality of the information obtained, whether from commercial sites or from free professional sites such as PubMed. Published articles provide helpful tips on how a busy practitioner can search a database such as MEDLINE and narrow the results to only high quality randomized controlled trials (RCTs). Researchers have found that the use of filters can provide clinicians with better searching strategies. The two most prominent filters being researched are content filters and validity filters. Content filters are specific to the drug or disease state being searched and ensure that the clinician is searching the most appropriate content. For example, an advanced search in PubMed involving MeSH headings will show that if the search is for regional enteritis, “Crohn’s disease” is a better content filter. In the IDIS system, the disease index would indicate that “enteritis, regional” would be the more appropriate term. Likewise, if searching for antibiotics for otitis media, the search term “antibiotics” would not be a good content filter because the databases are searched for just that term and not necessarily a specific type of antibiotic. PubMed and MEDLINE allow the researcher to explode terms like antibiotics to get better content results. Validity filters are a means to narrow the search to only the highest-quality studies. Terms such as “randomized controlled trial” or “double-blind” can be used to eliminate studies of weaker methodology. In a recent study, pharmacy students provided with content and validity filters demonstrated improved searching abilities and identified more articles on evidence-based medicine (EBM) than students searching without these filters. For the busy practitioner, proper training on how to search secondary databases with the use of content and validity filters can produce DI answers in less time and with better-quality evidence.

PHARAMACOKINETICS

*Pharmacokinetics*is currently defined as the study of the time course of drug absorption, distribution, metabolism,and excretion. *Clinical pharmacokinetics* is the application of pharmacokinetic principles to the safe and effective therapeutic management of drugs in an individual patient. Primary goals of clinical pharmacokinetics include enhancing efficacy and decreasing toxicity of a patient’s drug therapy. The development of strong correlations between drug concentrations and their pharmacologic responses has enabled clinicians to apply pharmacokinetic principles to actual patient situations. A drug’s effect is often related to its concentration at the site of action, so it would be useful to monitor this concentration. Receptor sites of drugs are generally inaccessible to our observations or are widely distributed in the body, and therefore direct measurement of drug concentrations at these sites is not practical. For example, the receptor sites for digoxin are thought to be within the myocardium. Obviously we cannot directly sample drug concentration in this tissue. However, we can measure drug concentration in the blood or plasma, urine, saliva, and other easily sampled fluids (Figure 1-1). *Kinetic homogeneity* describes the predictable relationship between plasma drug concentration and concentration at the receptor site where a given drug produces its therapeutic effect (Figure 1-2). Changes in the plasma drug concentration reflect changes in drug concentrations at the receptor site, as well as in other tissues. As the concentration of drug in plasma increases, the concentration of drug in most tissues will increase proportionally. Similarly, if the plasma concentration of a drug is decreasing, the concentration in tissues will also decrease. Figure 1-3 is a simplified plot of the drug concentration versus time profile after an intravenous drug dose and illustrates this concept.

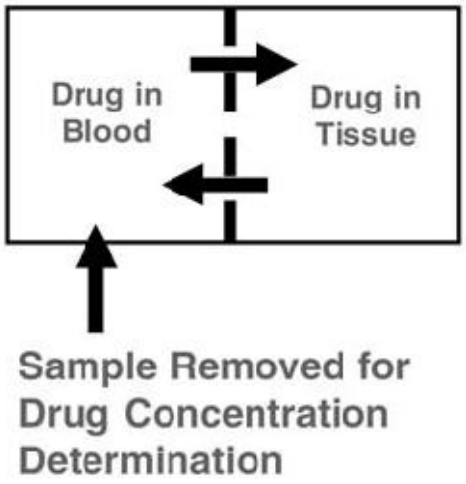


FIGURE 1-1.Blood is the fluid most often sampled for drug concentration determination.

The property of kinetic homogeneity is important for the assumptions made in clinical pharmacokinetics. It is the foundation on which all therapeutic and toxic plasma drug concentrations are established. That is, when studying concentrations of a drug in plasma, we assume that these plasma concentrations directly relate to concentrations in tissues where the disease process is to be modified by the drug (e.g., the central nervous system in Parkinson's disease or bone in osteomyelitis). This assumption, however, may not be true for all drugs.

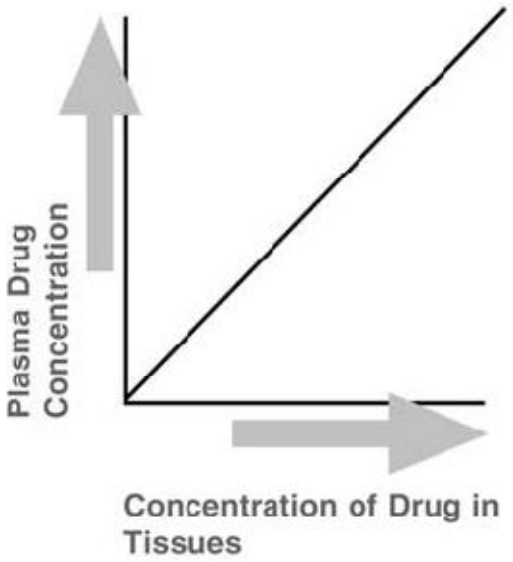


FIGURE 1-2.Relationship of plasma to tissue drug concentrations

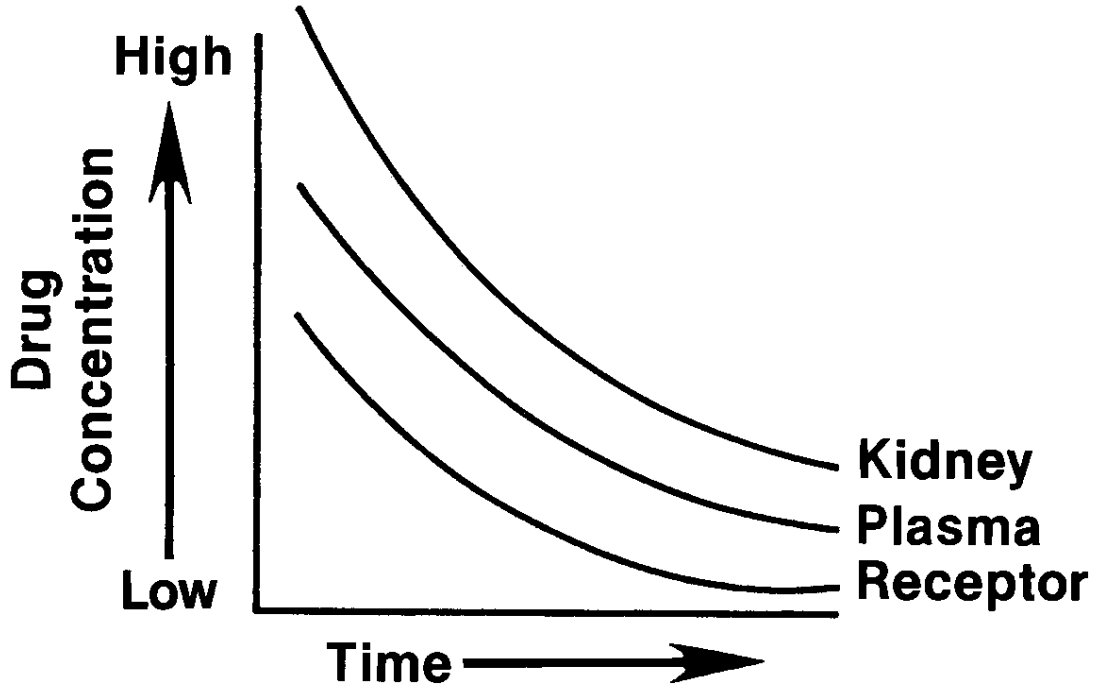
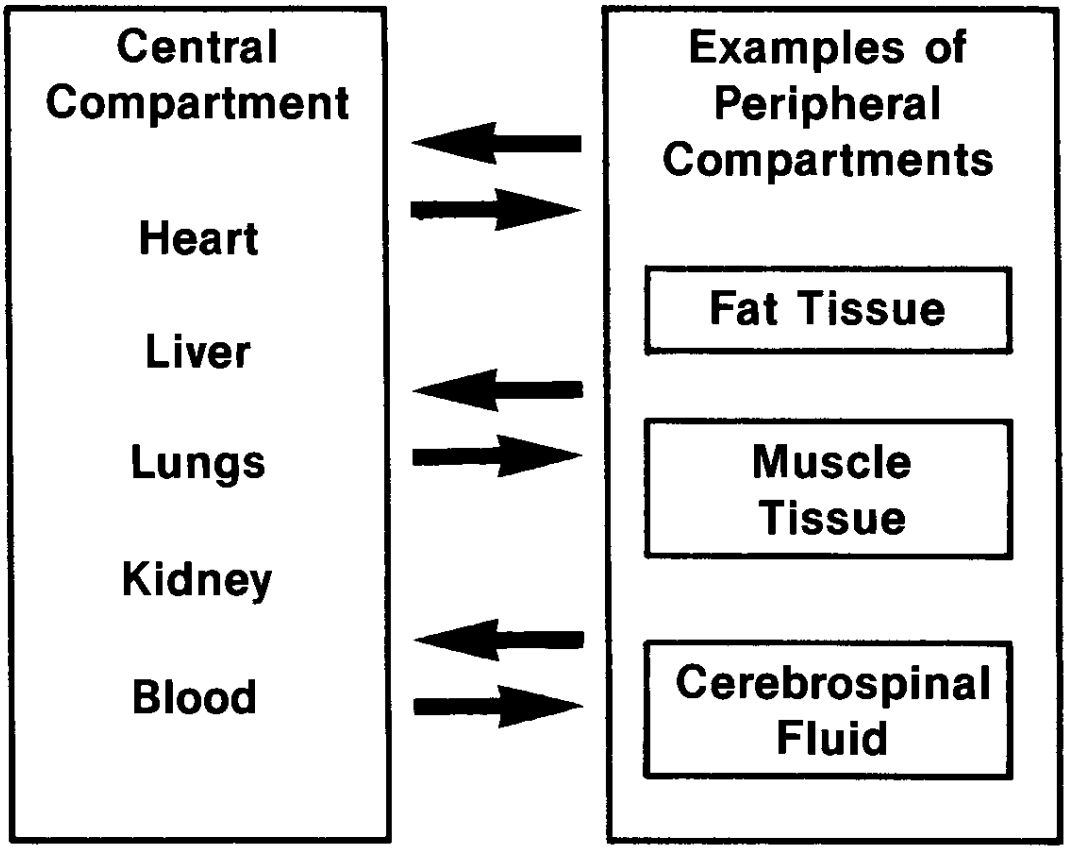


FIGURE 1-3.Drug concentration versus time

Pharmacokinetic Models:

The handling of a drug by the body can be very complex, as several processes (such as absorption, distribution, metabolism, and elimination) work to alter drug concentrations in tissues and fluids. Simplifications of body processes are necessary to predict a drug's behavior in the body. One way to make these simplifications is to apply mathematical principles to the various processes. To apply mathematical principles, a model of the body must be selected. A basic type of model used in pharmacokinetics is the compartmental model. Compartmental models are categorized by the number of compartments needed to describe the drug's behavior in the body. There are one-compartment, two-compartment, and multicompartment models. The compartments do not represent a specific tissue or fluid but may represent a group of similar tissues or fluids. These models can be used to predict the time course of drug concentrations in the body. Compartmental models are termed *deterministic* because the observed drug concentrations determine the type of compartmental model required to describe the pharmacokinetics of the drug. This concept will become evident when we examine one- and two-compartment models. To construct a compartmental model as a representation of the body, simplifications of body structures are made. Organs and tissues in which drug distribution is similar are grouped into one compartment. For example, distribution into adipose tissue differs from distribution into renal tissue for most drugs. Therefore, these tissues may be in different compartments. The highly perfused organs (e.g., heart, liver, and kidneys) often have similar drug distribution patterns, so these areas may be considered as one compartment. The compartment that includes blood (plasma), heart, lungs, liver, and kidneys is usually referred to as the *central compartment* or the *highly blood-perfused compartment*. The other compartment that includes fat tissue, muscle tissue, and cerebrospinal fluid is the peripheral compartment, which is less well perfused than the central compartment. Another simplification of body processes concerns the expression of changes in the amount of drug in the body over time. These changes with time are known as *rates*. The elimination rate describes the change in the amount of drug in the body due to drug elimination over time. Most pharmacokinetic models assume that elimination does not

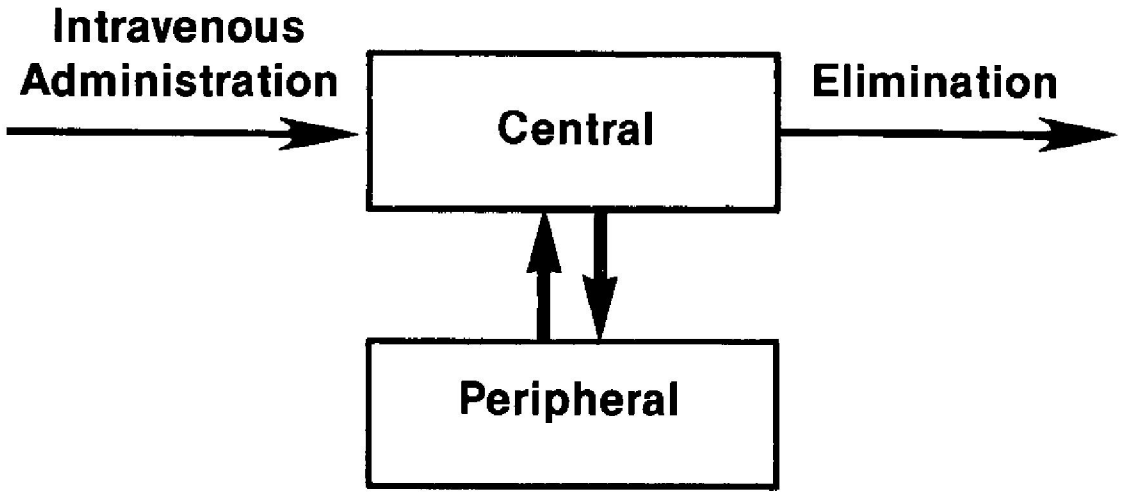
change over time. The value of any model is determined by how well it predicts drug concentrations in fluids and tissues. Generally, it is best to use the simplest model that accurately predicts changes in drug concentrations over time. If a one-compartment model is sufficient to predict plasma drug concentrations (and those concentrations are of most interest to us), then a more complex (two-compartment or more) model is not needed. However, more complex models are often required to predict tissue drug concentrations.



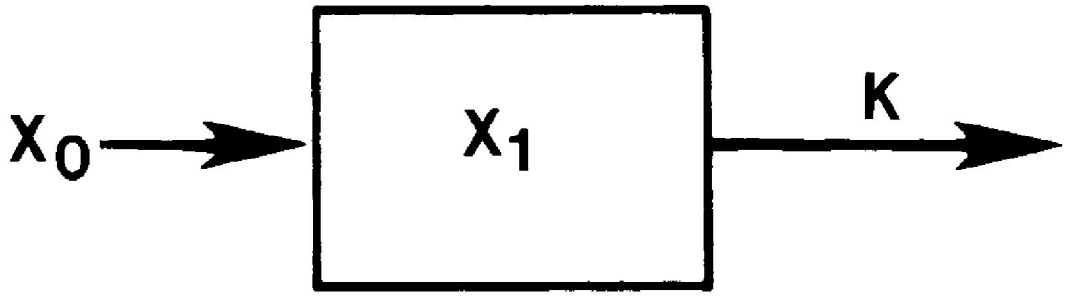
Typical organ groups for central and peripheral compartments

Compartmental Models:

The one-compartment model is the most frequently used model in clinical practice. In structuring the model, a visual representation is helpful. The compartment is represented by an enclosed square or rectangle, and rates of drug transfer are represented by straight arrows. The arrow pointing into the box simply indicates that drug is put into that compartment. And the arrow pointing out of the box indicates that drug is leaving the compartment. This model is the simplest because there is only one compartment. All body tissues and fluids are considered a part of this compartment. Furthermore, it is assumed that after a dose of drug is administered, it distributes instantaneously to all body areas. Some drugs do not distribute instantaneously to all parts of the body, however, even after intravenous bolus administration. *Intravenous bolus dosing* means administering a dose of drug over a very short time period. A common distribution pattern is for the drug to distribute rapidly in the bloodstream and to the highly perfused organs, such as the liver and kidneys. Then, at a slower rate, the drug distributes to other body tissues. This pattern of drug distribution may be represented by a two-compartment model. Drug moves back and forth between these compartments to maintain equilibrium.

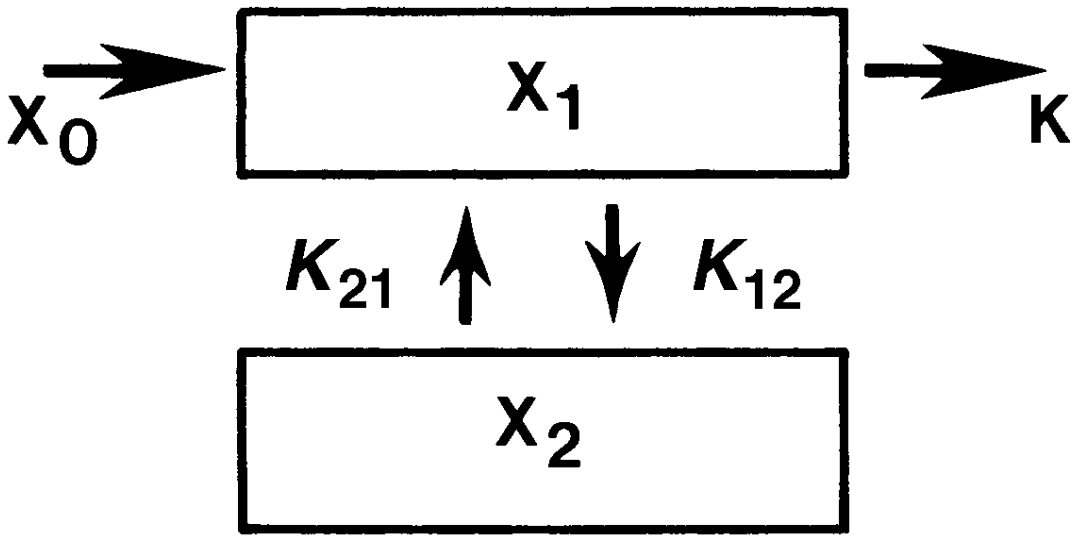


Compartmental model representing transfer of drug to and from central and peripheral compartments



Where: X_0 = Dose of drug
X_1 = Amount of drug in body
K = Elimination rate constant

One-compartment model



where:
X_0=dose of drug
X_1= amount of drug in central compartment
X_2= amount of drug in peripheral compartment
K= elimination rate constant of drug from central compartment to outside the body
K_{12}= elimination rate constant of drug from central compartment to peripheral compartment
K_{21}= elimination rate constant of drug from peripheral compartment to central compartment

Two-compartment model

HOSPITAL AND CLINICAL PHARMACY

Clinical pharmacy is defined as the branch of pharmaceutical science dealing with utilization of pharmacist knowledge, skills and judgments related to biomedical and pharmaceutical sciences, to prove the safety, the cost and the precision of the drug usage in the patient care.

Clinical pharmacy has emerged as one of the latest branches of pharmacy in 21st Century. It is where pharmacists deal with various aspects of patient care, dispensing of drugs and advising patients on the safe and rational use of drugs. It can also be explained as a part of pharmacy in which the clinical pharmacist provides patient care that optimizes the use of medication and promotes health, wellness, and disease prevention. To elaborate the story we can say that clinical pharmacy is to use drug control and the effective application of the knowledge. Professional skills and ethics assure the optimal safety in the distribution and use of medicine. The purpose of the Professional Education in Clinical Pharmacy and Public Health is to qualify each pharmaconomist (expert in pharmaceuticals) to practice clinical pharmacy at a higher and more professional level. Hence, ensures the patient's maximum well-being during the drug therapy. Clinical pharmacy describes the new role of the 21st Century's pharmacists. It doesn't restrict the role of a pharmacist merely to good manufacture practices, easy procurement, proper preparation, distribution and control of drug products. In addition, it also comprises functions necessary to discharge a particular set of social responsibilities related to proper therapeutic use of drugs in the aspects like prescribing, dispensing and administrating drugs, documenting professional services, direct patient involvement, Reviewing drug use, Education, Consultation and Counseling. The aim of clinical pharmacy practice is to ensure the patient's maximum well-being and to play a meaningful role in the safe and rational use of the drugs. These goals are to enable the physician do a better job of prescribing and monitor the drug therapy for patient. Further, to help the medical and para-medical staff to enable effective drug therapy. Clinical pharmacy practice also

deals with proper maintenance of the documentation regarding the medication incidents effectively to maximize the patient's compliance in drug use process.

Building up a Clinical Pharmacist Internationally, particularly in the countries like the US, Canada, Australia etc clinical pharmacists have extensive education in the biomedical, pharmaceutical, socio-behavioural and clinical sciences. Most clinical pharmacists have a Doctor of Pharmacy (Pharm.D.) degree and many have completed one or more years of post-graduate training (e.g. a general and/or specialty pharmacy residency). Many clinical pharmacists also choose to become Board Certified through the Board of Pharmacy Specialties (BPS) which was organized in 1976 as an independent certification agency of APhA (American Pharmacists Association). A pharmacist may become a Board Certified Pharmacotherapy Specialist (BCPS), a Board Certified Oncology Pharmacist (BCOP), Board Certified Nuclear Pharmacist (BCNP), Board Certified Nutrition Support Pharmacist (BCNSP), or a Board Certified Infectious Disease. It is denoted as an "Added Qualification" or AQ. In order to obtain one of these specialties you must first be a Board Certified Pharmacotherapy Specialist and then submit a portfolio to the Board of Pharmacy Specialties for review to determine if they will grant you the added qualifications.

In India, M.Pharm (Clinical Pharmacy) is a two-year post graduate Psychiatric Pharmacist (BCPP) through the Board of Pharmacy Specialties (BPS). There are also sub specialties within the Pharmacotherapy specialty: Cardiology and degree course, after B.Pharm. In this course, the Graduates of Pharmacy are provided with the opportunity to acquire knowledge about all the tasks performed by a pharmacist in hospitals, nursing homes, clinics or any other such places. The course focuses on the study of the patterns of use and effects of drugs on patients and deal with the correct and appropriate use of medicinal products and devices. In order to seek admission into the course, one has to appear for GATE/GPAT Entrance examination or any other State or University entrance examination.

Qualities of clinical pharmacist Clinical pharmacists care for patients in all health care settings but the clinical pharmacy movement initially began inside hospitals and clinics. Often collaborate with physicians and other healthcare professionals. Pharmacists should be well-versed with the common language used by the people in order to communicate with the patient and co-professionals easily and effectively. Pharmacists are also expected to have thorough knowledge of the etiology of the disease, its signs, symptoms, pathophysiology, diagnostic tests, pharmacokinetics, etc. Proper clinical training should be given to the clinical pharmacist to provide information regarding rational drug use, drug therapy and drug doses. [6]
Condition for a clinical pharmacy -A clinical pharmacy professional should appreciate the role of medical and para-medical staff. There should be enough bondage between the physician and the pharmacist to visit the patients together. All of the medical staff should develop an inter-professional relationship to enhance the quality of patient care. Further, there should be a deep sense of responsibility in the clinical pharmacist with respect to medical care. It helps in maintaining proper patient history and gaining confidence. As drug therapy is an ongoing process it needs to be checked by the clinical pharmacist timely. It may be changed according to the patient's condition and requirement.

Health care team and a clinical pharmacist There are certain laid roles and responsibilities of a clinical pharmacist in a health care team that consists of several medical and para-medical professionals. These responsibilities should be executed by the clinical pharmacist with immense care. The clinical pharmacist should interact with the patients and maintain their complete and exhaustible medical history. The clinical pharmacist should also do proper documentation of the hypersensitivities or allergy to certain drugs, food habits, drug dependence or intoxications to certain chemical substances, side effects of some drugs, incorrect drug administration, etc about

the patient. The prescribed drugs may interact with certain OTC drugs; therefore, after receiving the prescription the clinical pharmacist should check the patient's medical history for drug related interactions and patient's habits. This helps in effective and accurate medical therapy. In the selection of a proper drug product/generic formulation (depending on the bio-availability and equivalence of such products) the clinical pharmacist can help the physician. Clinical pharmacist can help in monitoring of drug therapy to ensure safety and efficacy. Monitoring of the drug therapy is very important particularly for those drugs that have narrow therapeutic index or administered chronically.[8]Various pharmacokinetic parameters can also be checked by the clinical pharmacist based on: plasma concentration of drug, enzymes and measurement of glucose quantity in blood, etc.

Patients with kidney impairment or hepatic disorders are more prone to adverse drug reactions. Clinical pharmacist can help in detection, prevention and reporting of adverse drug reactions. He may advice the physician for alternate drug therapy for the concerned patients. Clinical pharmacists may play a major role in designing health and drug policies, and assist as a source of information for the health care professionals and to the public. The drug management greatly relies on the clinical pharmacist to check the selection, requirement, procurement, distribution and use of the drugs. Also, Research and development in the field of biological availability of active ingredients requires active participation by the clinical pharmacists. The clinical pharmacist can help in executing clinical trials and based on standard principles and bio-statistical evaluation. A clinical pharmacist is an expert to provide detailed information to the health professionals and the general public. Effective selection, utilization and retrieval of drug literature by the clinical pharmacist can enable in the proper understanding of the facts by the medical team. He can also abstract information from periodic bulletins, newsletters or other pharmacy literature.

Scope of clinical pharmacy in India In hospitals the services regarding clinical pharmacy are of considerable value because the concerned clinical pharmacist serves as a guide to the physician for safe and rational use of drugs. He also assists to achieve economy in the hospital by planning safe drug policies, suggestive means of reduction of waste, by preventing misuse or pilferage of drugs. In addition to it the preparation of preventing forecasting future drug requirements of the hospital, based upon their drug utilization patterns. Therefore, scope of clinical pharmacy covers areas to foster innovation, improve public health and provide a knowledge exchange. Clinical pharmacist enables rational drug use by providing correct drug information including the proper utilization of the drugs utilized as drug therapy, along with all the precautions to be taken as indicated or asked by the pharmacist or the physician. It discourages any irrational or reckless use of drugs and also, concerns with the procurement of the drugs into the market from the industry and their channelization to the patient for use. Clinical pharmacy also deals with ensuring safety and efficacy of the drugs after marketing. Safety can be evaluated by means of non-experimental research, whereas evaluation of efficacy in a variety of settings representing normal medical practice generally requires experiments, randomized and blinded. National or International markets are flooded with tens of drug combinations, low therapeutic value products or duplicate brand names. Thus, under this study it is clarified how to choose the correct drug for administration or treatment.

BARCODE MEDICINE IDENTIFICATION AND AUTOMATED DISPENSING OF DRUGS

In December 2001 the Food and Drug Administration (FDA) published a notice notifying manufacturers and other interested parties that a regulation requiring bar code identification on medications was being considered. In June 2002 the FDA held a public hearing to hear comments about the requirements that should be included in the regulation. Representatives

from industry, health care, professional organizations, vendors, and patient safety advocates attended the meeting. A proposed rule was published in the Federal Register in March 2003 with comments being accepted until mid-June 2003. Requirements in the proposed regulation include:

• Linear bar code identification must be used on prescription drug labels, including OTC products commonly used in hospitals;
• Sample medications are excluded from the requirement;
• Bar code identification must be on the immediate container, as well as on any outer container, and;
• At a minimum, the bar code must contain the NDC number of the medication.

The FDA proposed rule also contained bar coding requirements for blood products and summarized the financial benefits resulting from decreased errors if the rule were imposed. Linear bar codes can be read with the available bar code scanners currently used in hospitals. To include bar code identification on smaller packages, such as small vials and ampules, it is necessary to use reduced space symbology (RSS), which may require upgrading scanners currently in use. If a requirement to include lot number and expiration date were also mandated, then a composite RSS would be required on the medications and additional upgrading of current scanners would be needed. Despite the need for hardware upgrades in scanning devices for some current users of bar coding, many patient safety advocates and professional organizations are recommending that the proposed FDA rule include lot number and expiration date on bar codes. Two-dimensional symbologies such as DataMatrix would be ideal for including the NDC number, lot number, and expiration date on all package sizes. This symbology is not considered a bar code but rather a digital identifier. Imaging scanners would be necessary to read these two-dimensional identifiers.

Many manufacturers and group purchasing alliances are already assisting hospitals in the adoption of BCMA.Several manufacturers have already committed to providing bar code identification on many of their products. Labeling and packaging vendors have begun to offer bar coding capabilities for the software used by hospitals to repackage medications. Group purchasing alliances have notified manufacturers that products which contain bar code identification will be preferred or even required in awarding contracts. A recent survey by the American College of Health Executives reported that 55% of respondents said drug bar coding was a technology they would consider within the next one to two years.3 This group also felt that bar code technology would have a positive impact on quality and would decrease overall costs. In a survey done by the Institute for Safe Medication Practices (ISMP), almost 90% of respondents reported that they would pay extra for medications that had bar coded unit dose medication packages, and almost half said they were actively considering BCMA. Others have been less enthusiastic about this technology. The Pharmaceutical Research and Manufacturers of America(PhRMA) have already asked for an exception for "small" labels. The United States Pharmacopeia (USP) is seeking an exception for vials and ampules less than 5 mL, despite the fact that some manufacturers have already begun to provide linear bar codes on these products. In addition, clinicians sometimes develop workaround that reduce the effectiveness of this technology.

Prevention of Errors with Bar Coding:

ISMP has reported many transcription,dispensing, and administration errors that could have been prevented with the use of BCMA. Currently, because of the checks and balances in the medication use system, the interception of prescribing errors is more than 50%, but less than 2% for drug administration errors. Examples of these types of potential and actual errors have been reported in the ISMP *Medication Safety Alert!* Errors resulting from look-alike packaging of IV solutions and unit dose syringes could be prevented by the use of bar code identification technology to verify that the medication to be administered is the same as

the one on the patient's medication administration record. The use of bar code technology will not prevent all medication errors and it does not detect prescribing errors, but it will have a positive impact when used with other technologies in safeguarding the system.

MOBILE TECHNOLOGY AND ADHERENCE MONITORING

Medication non-adherence is a prevalent, complex problem. Failure to follow medication schedules may lead to major health complications, including death. Proper medication adherence is thus required in order to gain the greatest possible drug benefit during a patient's treatment.Interventions have been proven to improve medication adherence if deviations are detected.This review focuses on recent advances in the field of technology-based medication adherence approaches and pays particular attention to their technical monitoring aspects. The taxonomy space of this review spans multiple techniques including sensor systems, proximity sensing, vision systems,and combinations of these. As each technique has unique advantages and limitations, this work describes their trade-offs in accuracy, energy consumption, acceptability and user's comfort, and user authentication.

Human lifespans will continue increases as the average quality of life improves. Evidence of this can be seen in recent reports that highlight the significant increase in aging population, especially in developed countries. As one would anticipate, the global population of people aged 60 years and older will grow by 250% in 2050 as compared to 2013. Likewise, as society ages, long-term healthcare expenditures are projected to increase. In order to maintain a healthy aging population,the employment of Assistive Health Technology (AHT) increases. Based on this, great efforts are being made towards achieving greater expectations of the quality in healthcare systems. There is no doubt that rapid technological advances will revolutionize research in the 21st century in a number of disciplines; namely human health. New approaches to monitor human health, behavior,and activity will be enabled. Medication adherence is an important component of health and well-being, with voluminous studies showing the importance of adequate medication adherence. Achieving healthy aging is challenging and thus requires several important strategies. Undoubtedly, correct medication is one of these strategies that are mainly related to the individual's behavior. In addition, it is well-known that medications are the primary approach for treating most illnesses. Hence, it requires the individual to take the medication as directed by the healthcare professional. However, medication adherence remains a common issue within the healthcare sector, and especially among older adults. In fact, more than 50% of the older people are living with multiple chronic illnesses. Thus, routine monitoring and assessment of the individual's adherence is crucial to improve their health outcomes.To be successful, this should be performed using accurate assessment methods. Current assessment methods of medication adherence have advantages as well as limitations. The main objective of the current article is to provide insights into what has been happening with respect to medication adherence monitoring technologies and address open research challenges for further improvement.

Medication Adherence:

Medication adherence can be defined as the extent to which a person-taking medication adheres to a self-administered protocol. In other words, medication adherence refers to the medication-intake behavior of the patient conforming to an agreed medication regimen specified by the healthcare provider with respect to timing, dosage, and frequency. From another point of view, non-adherence refers to the failure of taking medication as prescribed, including in-consistency,missing doses, and failing to re-fill the medication. Nonetheless, studies showed that failure to meet the medication-intake regime can result in emergence of drug resistance, accelerated progression of disease, many irrevocable health complications, and increased mortalities. The benefits of adhering tomedication regimens aremany. However, for the patient, high adherence to prescribed medication leads to less health complications, more treatments' benefits, and potentially active drug effect in the case of completely treated infectious disease. Another benefit is that medication adherence helps in

minimizing drug wastage and reducing healthcare costs. On the other side, poor medication adherence proven to come with degradation in the health of the patient that may potentially lead to substantial disability or death, especially for patients that are chronically ill.

Medication Adherence Monitoring:

Solutions to non-adherence demand the contribution ofmultiple factors. Nonetheless, the effectiveness and reliability of the monitoring method is central to achieving large improvements in adherence. Manual approaches require the attention and effort of the patient. Direct biochemical approaches require the patient to report to a clinic for fluid testing. In addition, the interventions associated with biochemical measurements, especially blood sample drawing, are of great burden for patients. The development of Cyber-Physical Systems (CPS) for healthcare is advancing rapidly. More recently, such systems included few sensing and monitoring devices associated with mobile devices such as smart pill bottles, smart watches, smart phones, and wearables. The combination of these smart monitoring devices with interventions that remind the patient in case a deviation is detected has proven to improve medication adherence. Compared to manual approaches,electronic-based approaches can reduce the cost and effort from the user's interest. In addition,the accuracy of adherence measure, which is of great importance from the healthcare provider's point of view can be enhanced when using electronic-based systems. Furthermore, as we live in the era of the Internet of Things (IoT), where everything is connected to the Internet, a connected health paradigm is becoming a more dominant field. One expectation of connected health is the automated capability of communicating the collected adherence measurements to the provider,and the feature of issuing reminder and alert messages based on the processed information.Moreover, electronic measurement systems can be portable and thus provide timely and long-term monitoring without restricting the user's mobility. In spite of the fact that electronic-based modalities can outperform traditional ones, the majority of electronic-based approaches come with limitations that act as burdens on the users, as we will see in Section 5. In fact, some of them have not achieved much success due to these burdens. Based on this, we conclude that there is no optimal electronic-based solution for medication adherence evaluation and, for that, much additional efforts will be required to realize accurate, low cost electronic adherence monitoring. Nonetheless, technological interventions are believed to be supportive tools in improving adherence. This is due to the fact that they allow timely monitoring, and generate useful information about the patient's behavior for the healthcare provider. To date, a considerable number of systems have been proposed and developed that utilize monitoring and tracking techniques in various health-related projects, including medication adherence monitoring.

Personal mobile device technology has witnessed a rapid progression in recent years. The services brought by mobile devices, such as the different means of communications and user applications, have enabled a host of possibilities. Thus, mobile applications' industry have been in race, including those for promoting healthcare of older patients. Specifically, many mobile and tablet based applications have been developed for medication adherence in the form of automated reminder systems. In this context, the sensor-app approach blends the use of sensor networks and mobile-app approaches for medication adherence tracking and monitoring. Abbey et al. developed a pillbox containing multiple compartments with ambient light sensor fixed in each of them and a WiFi connection. Also, a mobile app has been developed that contains the medicine schedule. The pillbox and the mobile app are interconnected through an online data source. Hence, the mobile app generates alarms when it is the time of medication until the patient takes the medication from the pillbox or chooses to delay the action. In a recent study, Boonnuddar and Wuttidittachotti proposed a pillbox-based system that uses the Arduino UNO WiFi and a load cell. Medication weight changes were reported to a server via the Internet. Also, a mobile application was developed that tracks the change in weight measurements and alerts the patient to take medication, if weight change is not detected. The system was tested for 160 times of medication taking and the accuracy of the mobile application notification functionally was 96.88%.

PATIENT MONITORING SYSTEMS

Continuous measurement of patient parameters such as heart rate and rhythm, respiratory

rate, blood pressure, blood-oxygen saturation, and many other parameters have become a common feature of the care of critically ill patients. When accurate and immediate decision-making is crucial for effective patient care, electronic monitors frequently are used to collect and display physiological data. Increasingly, such data are collected using non-invasive sensors from less seriously ill patients in a hospital's medical-surgical units, labor and delivery suites, nursing homes, or patients' own homes to detect unexpected life-threatening conditions or to record routine but required data efficiently.We usually think of a **patient monitor** as something that watches for—and warns against—serious or life-threatening events in patients, critically ill or otherwise. **Patient monitoring** can be rigorously defined as "repeated or continuous observations or measurements of the patient, his or her physiological function, and the function of life support equipment, for the purpose of guiding management decisions, including when to make therapeutic interventions, and assessment of those interventions". A patient monitor may not only alert caregivers to potentially life-threatening events; many also provide physiologic input data used to control directly connected lifesupport devices.

Patient Monitoring in Intensive-Care Units

There are at least five categories of patients who need physiological monitoring:

1. Patients with unstable physiological regulatory systems; for example, a patient whose respiratory system is suppressed by a drug overdose or anesthesia
2. Patients with a suspected life-threatening condition; for example, a patient who has findings indicating an acute myocardial infarction (heart attack)
3. Patients at high risk of developing a life-threatening condition; for example, patients immediately after open-heart surgery or a premature infant whose heart and lungs are not fully developed
4. Patients in a critical physiological state; for example, patients with multiple trauma or septic shock.
5. Mother and baby during the labor and delivery process.

Care of the critically ill patient requires prompt and accurate decisions so that lifeprotecting and life-saving therapy can be appropriately applied. Because of these requirements, ICUs have become widely established in hospitals. Such units use computers almost universally for the following purposes:

- To acquire physiological data frequently or continuously, such as blood pressure readings
- To communicate information from data-producing systems to remote locations (e.g., laboratory and radiology departments)
- To store, organize, and report data
- To integrate and correlate data from multiple sources
- To provide clinical alerts and advisories based on multiple sources of data
- To function as a decision-making tool that health professionals may use in planning the care of critically ill patients
- To measure the severity of illness for patient classification purposes
- To analyze the outcomes of ICU care in terms of clinical effectiveness and cost Effectiveness

Development of Computer-Based Monitoring:

Teams from several cities in the United States introduced computers for physiological monitoring into the ICU, beginning with Shubin and Weil (1966) in Los Angeles and then Warner and colleagues (1968) in Salt Lake City. These investigators had several motives: (1) to increase the availability and accuracy of data, (2) to compute derived variables that could not be measured directly, (3) to increase patient-care efficacy, (4) to allow display of the time trend of patient data, and (5) to assist in computer-aided decision-

making. Each of these teams developed its application on a mainframe computer system, which required a large computer room and special staff to keep the system operational 24 hours per day. The computers used by these developers cost over $200,000 each in 1965 dollars! Other researchers were attacking more specific challenges in patient monitoring. For example, Cox and associates (1972) in St. Louis developed algorithms to analyze the ECG for heart rhythm disturbances in real-time. The arrhythmiamonitoring system, which was installed in the coronary-care unit of Barnes Hospital in 1969, ran on a relatively inexpensive microcomputer. The advent of integrated circuits and other advances allowed computing power per dollar to increase dramatically. As hardware became smaller, more reliable, and less expensive, and as better software tools were developed,simple analog processing gave way to digital signal processing. Monitoring applications developed by the pioneers using large central computers now became possible using dedicated microprocessor-based machines at the bedside. The early bedside monitors were built around "bouncing-ball" or conventional oscilloscopes and analog-computer technology. As computer technology has advanced,the definition of **computer-based monitoring** has changed. The early developers spent a major part of their time deriving data from analog physiological signals. Soon the Patient-Monitoring Systems 591data-storage and decision-making capabilities of the computer monitoring systems came under the investigator's scrutiny. Therefore, what was considered computer-based patient monitoring in the late 1960s and early 1970s is now entirely built into bedside monitors and is onsidered simply a "bedside monitor." Systems with database functions,report-generation systems, and some decision-making capabilities are usually called **computer-based patient monitors**.

Current Issues in Patient Monitoring:

As more health services are shifted to outpatient settings, the acuity of hospitalized patients continues to increase; thus, the future of computer-based ICU monitoring systems is bright. Developments in bedside monitors have accelerated because of the availability of more powerful and affordable microcomputers. Nonetheless, some important areas of research in patient monitoring have not yet been addressed effectively.

Data Quality and Data Validation

There are still major problems with acquiring ICU data either automatically or manually. A system must provide feedback at various levels to verify correct operation, to carry out quality control, and to present intermediate and final results. As discussed earlier, some **cross validation** between signals is possible, but this process is performed by very few of the bedside monitors in use today. An ICU study of early, standalone pulse oximetry monitors revealed that up to 46.5 percent of low saturation alarms were neither observed nor responded to by any caregiver in large part due to constant false alarms associated with such devices. Some newer patient-monitoring devices, such as integrated pulse oximeters and direct pressure measuring systems, have built in noise-rejection algorithms to improve the quality of the data presented. Data validation, however, is one area of patient monitoring that still offers much opportunity for technological development and improvement.

Continuous Versus Intermittent Monitoring

To perform intermittent monitoring—periodic measurement of blood pH, for example—the overriding concerns in determining sampling rate are how rapidly the parameter can change, and how long before a dangerous change will result in irreversible damage. Sudden heart stoppage or severe dysrhythmias are the most frequent causes of sudden death. Therefore, heart-rate and rhythm monitors must function continuously and should sound alarms within 15 to 20 seconds after detecting a problem. Other physiological parameters are not as labile and can be monitored less frequently. For the most part, medical measurements are made intermittently, and even continuously measured parameters are displayed at intervals. For example, heart rate can change with each beat (by 0.35 to 1 second). To provide data that a human can interpret, however, a bedside monitor usually updates its display every 3 seconds.

Data Recording: Frequency and Quantity

In the past, because analog and early digital bedside monitors and central stations could not store continuous waveforms from all patients, it was acceptable for nurses to archive periodic strip chart recordings ("snapshots") in the patient's ICU chart. Most ICUs

have policies and procedures for pasting waveform recordings during the nursing shift and for critical events. The newer central stations, however, record digitized waveforms to hard disk on a continuous basis, and theoretically these data could be archived with the patient's electronic chart or printed out for a paper chart. But must second-bysecond waveform data be archived permanently? Will it improve the quality of patient care? Or will it simply increase the cost of care in the form of increased magnetic or optical storage media, paper usage, and material for lawyers to haggle over for years to come?

Invasive Versus Noninvasive Monitoring

Physiological and biochemical parameters commonly used in monitoring can be measured by instruments and devices that are either invasive (require breaking the skin or entering the body) or noninvasive. After several decades of development of **invasive techniques**, the recent trend has been to design **noninvasive methods**. Much of the Patient-Monitoring development of noninvasive technology can be attributed to the availability of microcomputers and solid-state sensors. The development of inexpensive light-emitting diodes (LED), small solid-state light detectors, and new computer methods made possible, for example, the development of the *pulse oximeter*, an exciting example of noninvasive monitoring technology. When alternately red and then infrared light is shined from the LEDs through a finger or an ear, the device can detect the pulsations of blood and determine arterial oxygen saturation and heart rate (Severinghaus & Astrup, 1986). Pulse oximetry is one of the most significant technological advances ever made in monitoring. The technology is quite reliable, yet inexpensive, and, because it is noninvasive, it does not subject the patient to the costs and risks of invasive techniques (e.g., infection and blood loss). Recently several manufacturers have produced "next-generation oximeters" (Health Devices 2003).

These newer pulse oximeters use advanced signal-processing algorithms that allow the devices to eliminate motion artifact and detect poor perfusion. As a consequence of these improvements, the quality of the derived signals and the number of false alarms have been dramatically reduced.

Integration of Patient-Monitoring Devices

Most bedside patient-support devices, such as IV pumps, ventilators, and physiological monitors, are microcomputer based. Each has its own display and, because each comes from a different manufacturer, each is designed as a standalone unit. As a result, it is common for a nurse or therapist to read a computer display from one of these devices and then to enter the data through a workstation into a different computer. The need to integrate the outputs of the myriad devices in the ICU is apparent. The absence of standards for medical-device communications has stymied the acceptance and success of automated clinical data management systems. Due to the large number and variety of medical devices available and to the peculiar data formats, it is impractical to interface the growing number of bedside devices to computers by building special software and hardware interfaces. The larger information challenges in the ICU now include integration of patient-monitoring data and observations charted by clinicians within ICU management systems and subsequent integration of the critical-care records with the overall computerized patient record.

PHARMA INFORMATION SYSTEM

The pharmacy information system (PIS) is usually a sub-system of the hospital information system (HIS). The PIS supports the distribution and management of drugs, shows drug and medical device inventory, and facilitates preparing needed reports. The PIS is a system that supports the distribution and management of drugs, identifying the type of intervention, determining the amount of inventory, reporting and managing of costs, and improving the accessibility of information. Furthermore, the PIS helps clinical decision-making by alerting users about clinically important drug-drug interactions, drug allergies and drug doses.It also evaluates patterns of drug use as well as other possible side effects of drugs. The PIS may operate as a separate and individual system or as part of a hospital information system(HIS), paired with the Computerized Physician Order Entry (CPOE) system. Accordingly, to ensure efficiency and effectiveness of these systems, evaluation of the PIS is

extremely important; this system could ultimately influence the safety and quality of care.
To identify and eliminate technical problems of health care systems, improve the efficiency and effectiveness of services,and minimize costs, careful evaluation of those systems is needed. In other words, the evaluation of information systems,as a key stage in the information system development life cycle can help to assure the technical capacity of these systems, determine the effects of using the systems on users practices, and allow application of modifications as required.

With respect to the security aspects of the PIS, all systems had the ability to report user activities based on IP address or individual user ID. However, the capability of restricting repeated unauthorized access attempts to systems was observed only in 40% of the systems. The password strength was the other security sub-criteria; the findings indicated that the passwords of the systems were not case-sensitive and did not require a combination of letters and numbers. The findings related to 'user friendliness' showed that all systems included some user friendliness features for pharmacy end-users. In this respect, all systems had the capability of displaying patients' drugs and emographic profiles completely and legibly; systems also had flexibility in sorting and selecting of commands from drug profiles, modifying the screen size, using multiple screens simultaneously for various activities, and using defaults to identify commands or a group of commands during order entry. Regarding the other general criteria, the findings showed that none of the pharmacy systems were connected to the national drug databank. It is notable that, in all five hospitals,the PIS was a sub-system of the integrated HIS and substantially interacted with other HIS sub-systems.

All of the studied systems had the ability to create reports of drugs and their dosages based on the physicians' name /and the prescription date. Furthermore, the systems had the capability to customize the list of medications and to exclude a drug from the list of current medications. However, the systems lacked functions such as showing the history of prescribed medication, prescribing drugs using different units,and renewing current medications without re-entering orders.The findings related to the 'patient safety management'showed that all five systems had the capability of identifying the drug dose and modifying medication orders. However,none of the systems had the functionality to display contraindications,drug interactions, adverse effects, or patient allergy to drugs.With respect to the 'purchase and sale management' function, none of the systems included the ability to order drugs electronically. However, all systems had the capability of calculating the prices for drugs and medical devices.

Findings related to 'drug stock management' showed that one of the systems lacked the stock management function. However, the other four systems had the capability of controlling drug entry to, and exit from, the pharmacy.In addition, these systems had the ability to check the minimum inventory for each drug and to create inventory alerts when a drug reached a minimum stock level. Regarding 'management reports' function of the systems,the findings indicated that all of the five PISs gave the system administrator the capability to create different reports using dynamic report builders. The reports included but were not limited to the total number of prescribed drugs for both inpatients and outpatients, daily drug distribution according to the delivery location, financial reports, and annual performance reports.

UNIT-IV

Bioinformatics

INRODUCTION

Bioinformatics has become a hot research topic in recent years, a hot topic in several disciplines that were not so closely linked with biology previously. A side evidence of this is the fact that the 2007 Graduate Summer School on Bioinformatics of China had received more than 800 applications from graduate students from all over the nation and from a wide collection of disciplines in biological sciences, mathematics and statistics, automation and electrical engineering, computer science and

engineering, medical sciences, environmental sciences, and even social sciences. So what is bioinformatics?

It is always challenging to define a new term, especially a term like bioinformatics that has many meanings. As an emerging discipline, it covers a lot of topics from the storage of DNA data and the mathematical modeling of biological sequences,to the analysis of possible mechanisms behind complex human diseases, to the understanding and modeling of the evolutionary history of life, etc. Another term that often goes together or close with bioinformatics is computational molecular biology, and also computational systems biology in recent years, or computational biology as a more general term. People sometimes use these terms to mean different things, but sometimes use them in exchangeable manners. In our personal understanding, computational biology is a broad term, which covers all efforts of scientific investigations on or related with biology that involve mathematics and computation. Computational molecular biology, on the other hand, concentrates on the molecular aspects of biology in computational biology, which therefore has more or less the same meaning with bioinformatics.

Bioinformatics studies the storage, manipulation, and interpretation of biological data, especially data of nucleic acids and amino acids, and studies molecular rules and systems that govern or affect the structure, function, and evolution of various forms of life from computational approaches. The word "computational" does not only mean "with computers," but it refers to data analysis with mathematical,statistical, and algorithmatic methods, most of which need to be implemented with computer programs. As computational biology or bioinformatics studies biology with quantitative data, people also call it as quantitative biology.

Most molecules do not work independently in living cells, and most biological functions are accomplished by the harmonic interaction of multiple molecules.In recent years, the new term systems biology came into being. Systems biology studies cells and organisms as systems of multiple molecules and their interactions with the environment. Bioinformatics plays key roles in analyzing such systems.People have invented the term computational systems biology, which, from a general viewpoint, can be seen as a branch of bioinformatics that focuses more on systems rather than individual elements.

For a certain period, people regarded bioinformatics as the development of software tools that help to store, manipulate, and analyze biological data. While this is still an important role of bioinformatics, more and more scientists realize that bioinformatics can and should do more. As the advancement of modern biochemistry, biophysics, and biotechnologies is enabling people to accumulate massive data of multiple aspects of biology in an exponential manner, scientists begin to believe that bioinformatics and computational biology must play a key role for understanding biology.

People are studying bioinformatics in different ways. Some people are devoted to developing new computational tools, both from software and hardware viewpoints,for the better handling and processing of biological data. They develop new models and new algorithms for existing questions and propose and tackle new questions when new experimental techniques bring in new data. Other people take the study of bioinformatics as the study of biology with the viewpoint of informatics and systems. These people also develop tools when needed, but they are more interested in understanding biological procedures and mechanisms. They do not restrict their research to computational study, but try to integrate computational and experimental investigations.

BIOINFORMATICS DATABASES

Primary sequence databases:

In the early 1980's, several primary database projects evolved in different parts of the world. There are two main classes of databases:DNA (nucleotide) databases and protein databases. The primary

sequence databases have grown tremendously over the years.Today they suffer from several problems, unpredicted in early years (when their sizes were much smaller):

- Databases are regulated by users rather than by a central body (except for Swiss-Prot).
- Only the owner of the data can change it.
- Sequences are not up to date.
- Large degree of redundancy in databases and between databases.
- Lack of standard for fields or annotation.

PIR - International Protein Sequence Database

PIR - The Protein Sequence Database was developed in the early 1960's. It is located at the National Biomedical Research Foundation (NBRF). Since 1988 it has been maintained by PIR-International

PIR currently contains 250,417 entries (Release 70.0, September 30, 2001). It is split into four distinct sections, that differ in quality of the data and the level of annotation:

Primary sequence databases 3

PIR1 - fully classified and annotated entries.
PIR2 - preliminary entries, not thoroughly reviewed.
PIR3 - unverified entries, not reviewed.
PIR4 - conceptual translations.

Swiss-Prot

Swiss-Prot was established in 1986. It is maintained collaboratively by SIB (Swiss Institute of Bioinformatics) and EBI/EMBL. Provides high-level annotations,including description of protein function, structure of protein domains, post-translational modifications, variants, etc. It aims to be minimally redundant. Swiss-Prot is linked to many other resources, including other sequence databases.

TrEMBL - Translated EMBL

Translated EMBL was created in 1996 as a computer annotated supplement to Swiss-Prot. It contains translations of all coding sequences in the EMBL nucleotide sequence database. SP-TrEMBL contains entries that will be incorporated into Swiss-Prot REM-TrEMBL contains entries that are not destined to be included in Swiss-Prot, (for example,T-cell receptors, patented sequences). The entries in REM-TrEMBL have no accession number.

GenPept

GenPept is a supplement to the GenBank nucleotide sequence database. Its entries are translation of coding regions in GenBank entries. They contain minimal annotation, primarily extracted from the corresponding GenBank entries. For the complete annotations, one must refer to the GenBank entry or entries referenced by the accession number(s) in the GenPept entry.

NRL 3D

NRL 3D is produced and maintained by PIR. It contains sequences extracted from the Protein DataBank (PDB). The entries include secondary structure, active site,binding site and modified site annotations, details of experimental method, resolution, Rfactor,etc. NRL 3D makes the sequence data in the PDB available for both text based and sequence-based searching. It also provides cross-reference information for use with the other PIR Protein Sequence Databases. For NRL 3D information, and sample entry.

DNA Databases (Nucleotide Sequences)

The growth rate of DNA databases is much higher than that of the protein databases. This is because most of the DNA is not coding for proteins and because DNA sequencing is the most prominent source of database entries.The large DNA databases are:Genbank (US), EMBL (Europe -

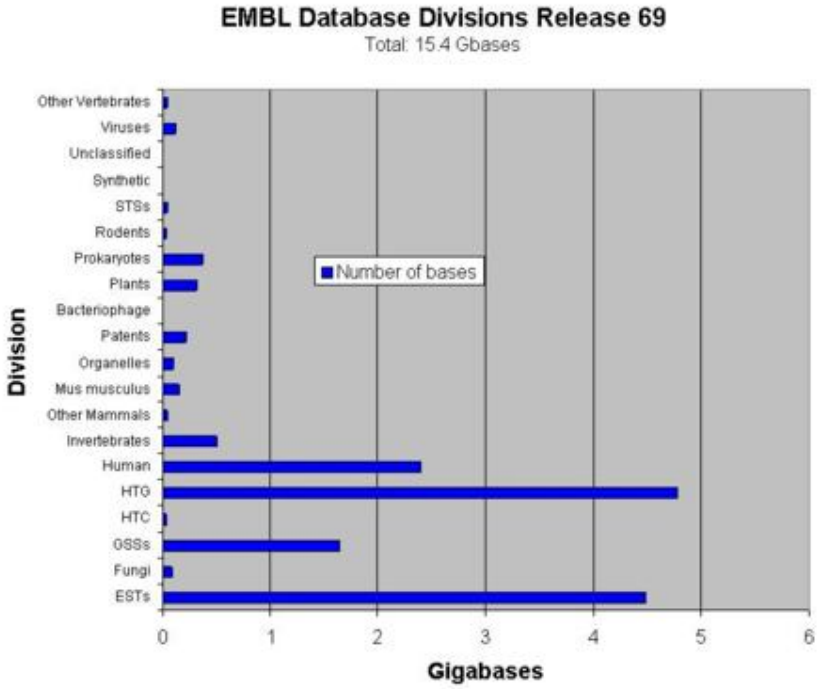
UK), DDBJ (Japan). These databases are quite similar regarding their contents and are updating one another periodically. This was is a result of the International Nucleotide Sequence Database Collaboration.

EMBL

EMBL is a DNA sequence database from European Bioinformatics Institute (EBI). EMBL includes sequences from direct submissions, from genome sequencing projects, scientific literature and patent applications. Its growth is exponential, on 3.12.01 it contained 15,386,184,380 bases in 14,370,773 records.

EMBL supports several retrieval tools:

SRS for text based retrieval and Blast and FastA for sequence based retrieval. EMBL is divided into several divisions.The division differ by the amount of sequences and by the quality of the data. See figure for division statistics.



GenBank

GenBank is a DNA sequence database from National Center Biotechnology Information (NCBI). It incorporates sequences from publicly available sources (direct submission and large-scale sequencing). Like EMBL it is also split into smaller, discrete divisions.This facilitates an efficient search.

Genome databases of specific organisms

These are smaller databases that present an integrated view of a particular biological system. Here, sequence data is only the first level of abstraction; It contains other levels of biological information. This leads to an overall understanding of the genome organization.

IMPACT OF BIOINFORMATICS IN VACCINE DISCOVERY

With the advent of computers and informatics, new approaches have been devised that facilitate vaccine research and development. Immunoinformatics targets the use of mathematical and computational approaches to address immunological questions. Since the 1980s,many immunoinformatics methods have been developed and used to predict T-cell and B-cell immune

epitopes. Indeed, many predicted T- and B-cell immune epitopes are possible epitope vaccine targets. Experimentally verified immune epitopes are now stored in web-based databases which are freely available for further analysis. Immune epitope studies are crucial to uncover basic protective immune mechanisms. A new era of vaccine research began in 1995, when the complete genome of *Haemophilus influenzae* (a pathogenic bacterium) was published. In parallel with advances in molecular biology and sequencing technology, bioinformatics analysis of microbial genome data has allowed *insilico* selection of vaccine targets. Further advances in the field of immunoinformatics have led to the development of hundreds of new vaccine design algorithms. This novel approach for developing vaccines has been named reverse vaccinology [8] or immunome-derived vaccine design. Reverse vaccinology was first applied to the development of vaccines against serogroup B *Neisseria meningitides* (MenB).With the availability ofmultiple genomes sequenced for pathogens, it is now possible to run comparative genomics analyses to find vaccine targets shared by many pathogenic organisms.In the postgenomics era, high throughput-omics technologies-genomics, transcriptomics, proteomics, and large-scale immunology assays enable the testing and screening of millions of possible vaccine targets in real time. Bioinformatics approaches play a critical role in analyzing large amounts of high throughput data at differing levels, ranging from data normalization, significant gene expression detection,function enrichment, to pathway analysis.Mathematical simulation methods have also been developed to model various vaccine-associated areas, ranging from analysis of host-Pathogen interactions and host-vaccine interactions to cost cost-effectiveness analyses and simulation of vaccination protocols. The mathematical modeling approaches have contributed dramatically to the understanding of fundamental protective immunity and optimization of vaccination procedures and vaccine distribution.Informatics is also changing postlicensure immunization policies and programs. Computerized immunization registries or immunization information systems (IIS) are effective approaches to track vaccination history. Bioinformatics has widely been used to improve surveillance of vaccine safety using systems such as the Vaccine Adverse Event Reporting System (VAERS, http://vaers.hhs.gov/) and the Vaccine Safety Datalink (VSD) project and vaccine effectiveness for each of the target vaccine preventable diseases via their respective public health surveillance systems. Computational methods have also been applied to model the impact of alternative immunization strategies and to detect outbreaks of vaccine preventable diseases and safety concerns related to vaccinations as well. With the large amounts of vaccine literature and data becoming available, it is not only challenging but crucial to perform vaccine literature mining, generate well-annotated and comprehensive vaccine databases, and integrate various vaccine data to enhance vaccine research. Computational vaccine literature mining will allow us to efficiently find vaccine information. To effectively organize and analyze the huge amounts of vaccine data produced and published in the postgenomics and information era, many vaccine-related databases, such as the VIOLIN vaccine database and analysis system (http://www.violinet.org/) and AIDS vaccine trials database (http://www.iavireport.org/trials-db/), have been developed and are available on the web. However, relational databases are not ideal for data sharing since different databases may use different schemas and formats. A biomedical ontology is a consensus-based controlled vocabulary of terms and relations, with associated definitions that are logically formulated in such a way as to promote automated reasoning. Ontologies are able to structure complex biomedical domains and relate themyriads of data accumulated in such a fashion as to permit shared understanding of vaccines among different resources. The Vaccine Ontology (VO; http://www.violinet.org/vaccineontology/) is a novel open-access ontology in the domain of vaccine. Recent studies show that VO can be used to support vaccine data integration and improve vaccine literature mining .

UNIT-V

Computers as data analysis in preclinical development

Chromatographic Data Analysis (CDS)

Analysis of pharmaceutical preparations by a chromatographic method can be traced back to at least the 1920s.By 1955, descending and ascending paper chromatography had been described in the *United States Pharmacopeia*(USP) for the identification of drug products. Subsequent editions introduced gas chromatographic and high-performance liquid chromatographic methods.

IMPURITIES

In the search for new drug candidates, scientists use molecular modeling techniques to identify potentially new structural moieties and screen natural sources or large families of synthetically related compounds, along with modifying exisiting compounds. Once a potentially new drug has been identified and is being scaled up from the bench to pilot plant manufacturing quantities, each batch is analyzed for identity, purity, potency, and safety. From these data, specifications are established along with a reference standard against which all future batches will be compared to ensure batch to batch uniformity.A good specification is one that provides for material balance. The sum of the assay results plus the limits tests should account for 100% of the drug within the limits of accuracy and precision for the tests. Limits should be set no higher than the level which can be justified by safety data and no lower than the level achievable by the manufacturing process and analytical variation. Acceptable limits are often set for individual impurities and for the total amount of drug-related impurities. Limits should be established for by-products of the synthesis arising from side reactions, impurities in starting materials, isomerization, enantiomeric impurities, degradation products,residual solvents, and inorganic impurities. Drugs derived from biotechnological processes must also be tested for the components with which the drug has come in contact, such as the culture media proteins (albumin,transferrin, and insulin) and other additives such as testosterone.This is in addition to all the various viral and other adventitious agents whose absence must be demonstrated.

A total impurity level of 2.0% has been adopted as a general limit for bulk pharmaceuticals. There have been no levels established for the presence of enantiomers in a drug substance/ product. This is primarily because the enantiomers may have similiar pharmacological and toxicological profiles, enantiomers may rapidly interconvert in vitro and/or in vivo, one enantiomer is shown to be pharmacologically inactive, synthesis or isloation of the perferred enantiomer is not practical, and individual enantiomers exhibit different pharmacologic profiles and the racemate produces a superior therapeutic effect relative to either enantiomer alone.For biotechnologically derived products the acceptable levels of foreign proteins should be based on the sensitivity/selectivity of the test method, the dose to be given to a patient, the frequency of administration of the drug, the source, and the potential immunogenicity of protein contaminants. Levels of specific foreign proteins range from 4 ppm to 1000 ppm.

The third category of drugs are phytotherapeutical preparations; 80% of the world population use exclusively plants for the treatment of illnesses. Chromatography is relied on to guarantee preparations contain therapeutically effective doses of active drug and maintain constant batch composition.A quantitative determination of active principles is performed when possible, using pure reference standards. In many phytotherapeutic preparations, the active constituents are not known, so marker substances or typical constituents of the extract are used for the quantitative determination.

Batch Selection

For both the drug substance (bulk drug) and drug product (dosage form) stability information from accelerated and long-term testing should be provided on at least three batches with a minimum of 12 months' duration at the time of submission.The batches of drug substance must be manufactured to a minimum of pilot scale which follows the same synthetic route and method of manufacturer that is to be used on a manufacturing scale. For the drug product,two of the three batches should be at least pilot scale. The third may be smaller. As

with the drug substance batches, the processes should mimic the intended drug product manufacturing procedure and quality specifications.

Storage Conditions

The stability storage conditions developed by the ICH are based on the four geographic regions of the world defined by climatic zones I ("temperate") and II ("subtropical"). Zones III and IV are areas with hot/dry and hot/humid climates, respectively.Long-term testing for both drug substance and product will normally be every 3 months, over the first year, every 6 months over the second year,and then annually. A significant change in stability for drug substance is when the substance no longer meets specifications. For the drug product, a significant change is when there is a 5% change in potency, exceeded pH limits, dissolution failure, or physical attribute failure. If there are significant changes for all three storage temperatures, the drug substance/product should be labeled "store below 250C." For instances where there are no significant changes label storage as 15-300C. There should be a direct link between the label statement and the stability characteristics. The use of terms such as ambient or room temperature are unacceptable

Biologies

Degradation pathways for proteins can be separated into two distinct classes; chemical and physical. Chemical instability is any process which involves modification of the protein by bond formation or cleavage. Physical instability refers to changes in the protein structure through denaturation,adsorption to surfaces, aggregation, and precipitation. Stability studies to support a requested shelf life and storage condition must be run under real-time, real-temperature conditions.The prediction of shelf life by using stability studies obtained under stress conditions and Arrhenius plots is not meaningful unless it has been demonstrated that the chemical reaction accounting for the degradation process follows first-order reaction.

METHOD VALIDATION

The ultimate objective of the method validation process is to produce the best analytical results possible. To obtain such results, all of the variables of the method should be considered, including sampling procedure, sample preparation steps, type of chromatographic sorbent, mobile phase, and detection. The extent of the validation rigor depends on the purpose of the method. The primary focus of this section will be the validation of chromatographic methods. The four most common types of analytical procedures are identification tests, including quantitative measurements for impurities, content,limit tests for the control of impurities, and quantitative measure of the active component or other selected components in the drug substance.

A. Specificity

The specificity of an analytical method is its ability to measure accurately an analyte in the presence of interferences that are known to be present in the product: synthetic precursors, excipients, enantiomers, and known (or likely) degradants that may be present. For separation techniques, this means that there is resolution of > 1.5 between the analyte of interest and the interferents. The means of satisfying the criteria of specificity differs for each type of analytical procedure: For identification, in the development phases, it would be proof of structure, whereas in quality control, it is comparison to a reference substance; for a purity test, to ensure that all analytical procedures allow an accurate statement of the content of impurities of an analyte; for assay measurements, to ensure that the signal measured comes only from the substance being analyzed.One practical approach to testing the specificity of an analytical method is to compare the test results of samples containing impurities versus those not containing impurities. The bias of the test is the difference in results between the two types of samples. The assumption to this approach is that all the interferents are known and available to the analyst for the spiking studies.

A more universal approach to demonstrating specificity of chromatographic methods has been outlined. For peak responses in highperformance liquid chromatography (HPLC), gas chromatography (GC),capillary electrophoresis (CE), or supercritical fluid chromatography

(SFC) or the spots (bands) in TLC or gel electrophoresis, the primary task is to demonstrate that they represent a single component. The peak homogeneity of HPLC and GC as well CE and SFC responses can be shown by using a mass spectrometer as a specific detector. The constancy of the mass spectrum of the eluting peak with time is a demonstration of homogeneity,albeit not easily quantified.Multiple ultraviolet (UV) wavelength detection has become a popular approach to evaluating chromatographic peak homogeneity. In the simplest form, the ratio between two preselected wavelengths is measured, and for a homogenous peak, the ratio remains constant. A ratio plot of pure compounds appears as a square wave, whereas an impurity distorts the square. This technique is most useful when the spectral properties of the overlapping compounds are sufficiently different and total chromatographic overlap does not occur. The ability to detect peak overlap can be enhanced by stressing (heat, light, pH, and humidity) the analyte of interest and evaluating the wavelength ratios. A degradation of 10-15% is considered adequate. The utility of this approach has been demonstrated for pipercuronium bromide. Potentially, additional information about peak purity can be obtained by recording UV-vis data at the upslope, apex, and downslope of a chromatographic response using photodiode array detection. An example of this approach has been published for a method used in assaying an analgesic. Peak purity can be assessed with a higher degree of certainty only by additional analysis using a significantly different chromatographic mode. The collected sample should also be analyzed by techniques that can be sensitive to minor structural differences such as nuclear magnetic resonance(NMR) spectroscopy.

B. **Linearity**

The evaluation of linearity can be best described as the characterization of the test method response curve. A plot of the test method response against analyte concentration is often expected to be linear over a specified range of concentrations. Some assays generate nonlinear curves.The function of the standard curve is to allow the prediction of a sample concentration interpolated from the standard data.This predictive feature does not require linearity of the assay response curve, but only that it be a reasonable description of the correlation between response and concentration. Attempting, a rigorous fit of a calculated curve fitting to the standard data may defeat the function because such rigorous curve fitting may emphasize the difference between the sample and the standard assay responses. The test method response curve is characterized by comparing the goodness of fit of calculated concentrations with the actual concentrations of the standards. For a linear response, this value would be the correlation coefficient derived from a linear regression using least squares. Nonlinear response curves require curve fitting calculations with the corresponding goodness-of-fit determinations. Plotting the test results graphically as a function of analyte concentration on appropriate graph paper may be an acceptable alternative to the regression line calculation.The range of an analytical method is the interval between the upper and lower level of analyte in the sample, for which it has been demonstrated that the method has a suitable level of precision, accuracy, and linearity.

C. **Limit of Measurement**

There are two categories within the level of measurement, the first is the limit of detection (LOD). This is the point at which a measured value is larger than the uncertainty associated with it; for example, the amount of sample exhibiting a response three times the baseline noise.The limit of detection is commonly used to substantiate that an analyte concentration is above or below a certain level, in other words, a limit test. The second category is referred to as the limit of quantitation. This limit is the lowest concentration of analyte in a sample that can be determined with acceptable precision and accuracy; for example, the lowest amount of analyte for which duplicate injections resulted in a relative standard deviation (RSD) of <2%. Limit of quantitation is commonly used for impurity and degradant assays of drug substances and products.The limit of measurement for an analyte is not a unique constant because of day-to-day variation in detector response. Extensive discussions of these limits have been published.

D. Precision (Random Error)

The precision of a test method expresses the closeness of agreement among a series of measurements obtained from multiple sampling of the same homogenous sample. The concept of precision is measured by standard deviations. It can be subdivided into either two or three categories. The European Community (EC) divides precision into repeatability and reproducibility. Repeatability expresses precision under conditions where there is the same analyst, the same equipment, a short interval of time, and identical reagents. This is also termed intra-assay precision. Reproducibility expresses the precision when the laboratories differ, when there are reagents from different sources, different analysts, tested on different days, equipment from different manufacturers, and so on. The Food and Drug Administration (FDA) uses a three-category definition of precision. The same definition is used by the EC and FDA for repeatability. The FDA differs from EC by the term "intermediate precision" which is determined within laboratory variation: different days, different analysts,different equipment, and so forth. Reproducibility expresses the precision between laboratories (collaborative studies). Several organizations differ in their approaches to collaborative studies: the United States Pharmacopeia uses procedures validated by pubic comment and ruggedness testing rather than a collaborative study process, whereas the International Union of Pure and Applied Chemistry's and AOAC Offical Methods of Analysis have developed harmonized procedures for collaborative studies.The reproducibility standard deviation is typically two to three times as large as that for repeatability. Precision decreases with a decrease in concentration. This dependence has been expressed as RSD = 2(1"°-5explogC),where RSD is expressed as a percentage and C is the concentration of the analyte. For the concentration ranges typically found in pharmaceutical dosage forms (1-10"3), the RSD under conditions of repeatability should be less than 1.0%, and less than 2.0% under conditions of reproducibility. These are similiar to the 1.5 % recommendation made for RSD of system repeatability after analyzing a standard solution six times. For method repeatability, which includes sample pretreatment, six replicate assays are made with a representative sample. A RSD no greater than 2% should be obtained.

E. Accuracy

Accuracy is the closeness of agreement between what is accepted as a true value (house standard, international standard) and the value found (mean value) after several replicates. This also provides an indication of systematic error. Two of the most common methods of determining accuracy are by comparing the proposed test procedure to a second test procedure whose accuracy is known and the recovery of drug above and below the range of use. Average recovery of the drug should be 98-102% of the theoretical value. Recoveries can be determined by either external or internal standard methods. Quantification by external standard is the most straightforward approach because the peak response of the reference standard is compared to the peak response of the sample. The standard solution concentration should be close to that expected in the sample solution. Peak responses are measured as either peak height or area.For the internal standard method, a substance is added at the earliest possible point in the analytical scheme. This compensates for sample losses during extraction, cleanup, and final chromatographic analysis. There are two variations in the use of the internal standard technique. One involves the determination of response factors which are the ratios of the analyte peak response to the internal standard peak response. The second is referred to as response ratios which are calculated by dividing the weight of the analyte by the corresponding peak response.An internal standard must be completely resolved from all other peak responses except where mass discrimination or isotopically labeled samples are used as the internal standard. The internal standard should elute near the solute to be quantified. The detector response should be similiar in area or height to the analyte of interest. The internal standard should be similar in terms of chemical and physical properties to the analyte being measured.Substances that are commonly used as internal standards include analogs,homologs, isomers, enantiomers, and isotopically labeled analogs of the analyte. The internal standard should not be present or be a potential degradant of the sample. Finally, the internal standard should be present in reasonably high purity.Internal standards are often used in dissolution testing of oral dosage

forms. Internal standards should be avoided in stability-indicating assays due to the possible coelution with unknown degradation products.

F. Ruggedness (Robustness)

The ruggedness of an analytical method is the absence of undue adverse influence on its reliability of performance by minor changes in the laboratory environment. This validation parameter is not recognized by all organizations with testing oversight, as this characteristic is implied by collaborative validation programs. The difference in chromatographic performance between columns of the same designation (i.e., C,g) is the most common source of chromatographic variability. To check the column-to-column ruggedness, the specificty(selectivity) of at least three columns from three different batches supplied by one column manufacturer should be checked. A similarly designated column from another manufacturer should also be evaluated.

System suitability Testing

After a method has been validated, an overall system suitability test should be routinely run to determine if the operating system is performing properly.An acceptable approach is to prepare a solution containing the analyte and a suitable test compound. If the method being used is to control the level of impurities, the minimum resolution between the active component and the most difficult to resolve impurity should be given. The chromatographic system should demonstrate acceptable resolution of the test solution and system precision.

A. System Resolution

There are several formulas available for calculating resolution factors. The formula recommended in USP 23 for GC and HPLC is as follows:

$$R = \frac{2(t_2 - t_.)}{W_2 + W_1}$$

where t2 and t, are the retention times of the two components and W2 and W1 are the corresponding widths at the peak base. The width is obtained by extrapolating the relatively straight sides of the peaks to the baseline.Some computer data systems have based their resolution calculations on the peak width at half the distance from the apex to the base of the peak. Peak widths have also been measured at the point of inflection.

B. Determination of System Precision

After a standard solution is injected a number of times, the relative standard deviation of the peak responses is measured as either the peak height or peak area. When using an internal standard method, the response ratio is calculated. Maximum allowable system related standard deviations made at the 99% confidence level have been tabulated. For the USP monographs,unless otherwise stated, five replicate chromatograms are used if the stated limit for relative standard deviation is 2% or less. Six replicate chromatograms are used if the stated relative standard deviation is more than 2.0%. The current USP emphasis is to perform all the replicate injections prior to sample assay and during testing whenever there is a significant change in equipment, or a critical reagent, or when a malfunction is suspected.Performing all the standard injections prior to sample assay has been controversial. The main point of contention is that the analyst does not have overall control of the chromatographic system from beginning to end. The recommendation is to periodically inject duplicate standard solutions which should agree to within 0.5% of their values. For planar techniques such as TLC or gel electrophoresis, this is a moot point because standards can be run alongside the samples in adjacent lanes. For example, when determining the the molecular homogeneity of proteins using SDSPAGE gel electrophoresis, the two outer lanes contain molecular-weight standards that bracket the expected masses with the reference standards of the protein of interest in the next inner lanes followed by the sample tracks in the inside lanes.

C. **Asymmetry Factor (Tailing Factor)**

If the peak to be quantified is asymmetric, a calculation of the asymmetry would also be useful in controlling or characterizing the chromatographic system. Peak asymmetry arises from a number of factors. The increase in the peak asymmetry is responsible for a decrease in chromatographic resolution, detection limits, and precision. Measurement of peaks on

solvent tails should be avoided.The peak asymmetry factor (tailing factor) can be calculated by several different methods.

D. Column Efficiency

The resolution factor is considered to be a more discriminating measure of system suitability than column efficiency. Yet, column efficiency determinations are required for the assay of antibiotics and antibioticcontaining drugs. The reduced plate height (hr) for the column is determined by first calculating the number of theoretical plates per column.

E. Column Capacity

The column capacity factor is calculated by

$$\kappa = \frac{tr - tm}{tm}$$

where the retention time of the solute is tr and the retention time of solvent or unretained substance is tm. The corresponding retention volume or distance can also be used, as they are directly proportional to retention time.

Product Testing

Product testing is one of the most important functions in pharmaceutical production and control. A significant portion of the CGMP regulations (21 CFR 211) pertains to the quality control and drug product testing.Out-of-specification laboratory results have been given additional emphasis by the FDA, particularly after the *Ban* v *FDA* court case.An out-of-specification result falls into three catogories: laboratory error,non-process-related or operator error, and process-related or manufacturing process error. Retesting of the same sample is appropriate when the analyst error can documented. An outlier test on some chemical assays,particularity those involving extensive sample preparation and manipulation,is justifiable but is not a routine approach to rejecting results.

There are numerous variables to consider in developing an accurate and rugged chromatorgaphic method. The extent depends on the purpose of the test: that is, stability-indicating assays are the most demanding, whereas identification tests are the least demanding.From the six validation variables listed, specificity, accuracy of dosage form assay, and ruggedness are the most crucial. In the initial stage of developing a chromatographic method, the primary goal is to measure an analyte in the presence of interferences. The second step is to demonstrate that the analyte can be accurately measured. The ruggedness and accuracy of a method can be improved with the development of treatment steps that require minimal manual manipulation and use of column packings that do not vary from lot to lot.The efforts at harmonization of the requirements among Europe, the United States, and Japan for methods validation, stability testing, and indentification of impurities are welcomed by all pharmaceutical analysts.

LABORATORY INFORMATION SYSTEM (LIMS)

A **laboratory information management system** (LIMS), sometimes referred to as a l**aboratory information system** (LIS) or **laboratory management system** (LMS), is a software based laboratory and information management system with features that support a modern laboratory's operations. Key features include — but are not limited to — workflow and data tracking support, flexible architecture, and data exchange interfaces, which fully "support its use in regulated environments". The features and uses of a LIMS have evolved over the years from simple sample tracking to an enterprise resource planning tool that manages multiple aspects of laboratory informatics.

The requirements specification

The requirements specification summarises the overall aims of the LIMS from the laboratories' viewpoint. It does not include any detail of how it is to be achieved. The importance of this document cannot be over emphasised, moreover, it is essential that the reader formulates his own ideas before approaching a potential supplier or developer of a system. Substantial planning has to go into this area to evaluate the

current as well as the future (2-3 years) requirements of the laboratory. The overall aim should be flexibility to accommodate present and future needs. At the fore-front of all thinking should be the question: what is to be done with the data or information? The purpose of this document is to allow potential suppliers of the LIMS to tender quotes.
In theory, the process of producing the requirements specification should be to step back and review the current working procedures within the laboratory with an open mind. However, the authors geared their LIMS to current work practices within the Department. Possible requirements have been outlined by Braithwaite. Furthermore, Liscouski recommends the use of pre-set criteria to measure the achievement of each objective. It is important to avoid using any jargon when writing the requirements specification because disciplinary boundaries will be crossed: if necessary define any keywords.The requirements specification should contain the following sections as a minimum:the structure and organisation of the department detailing the type of work, the number of samples assayed and the analytical instrumentation used. This document must also give an overview of the tasks the LIMS will be required to undertake and if connection to any existing computers is needed.

Objectives of the proposed Drug Analysis LIMS:
(1) Increase productivity.
(2) Compliance with Good Laboratory Practice regulations.
(3) Elimination of calculation and transcription errors.
(4) Automated generation of reports and integration with word processing.
(5) Help and speed the interpretation of data.
(6) Bar code labels for samples and rapid data entry.
(7) Verification of data entry.
(8) Flexible and expandable system.
(9) Sample tracking and scheduling.
(10) On-line access to historical analytical data.

The plans should be discussed with laboratory personnel; keeping them informed of developments and asking for feedback on proposals is a good way of building enthusiasm for the system. However, care should be exercised to ensure that the expectations of the laboratory staff, regarding the capabilities of the LIMS system and the timing of its delivery, are realistic. The laboratory staff should be made aware that this is the chosen method of approach, but it could vary depending on the systems available. Consultation with other Departments, who either submit samples or process the results, is also essential, both to keep them informed on developments and to consider any forthcoming suggestions.
In producing a requirements specification there are two possible approaches: the first would not radically change the working practices of the laboratory that have been built up over the past years. In essence, this tailors the LIMS to the laboratory. The second method tailors the laboratory to a LIMS and could be used as a way of implementing changes in the working practices. In either case, it is better to aim high and incorporate all the wishes of the laboratory into the specification and then debate with the supplier each point where the product on offer does not match the specification requested. Otherwise, the resulting system may be a disappointment.

The production of a requirements specification can be achieved by senior analytical staff if the information flow in the laboratory is relatively straightforward. Alternatively, computer consultants may be retained. However, they have to be briefed on the function of the laboratory and how it operates before they can begin to analyse the information pathways and make suggestions.

Consultants may offer new ideas and fresh approaches combined with experiences from different installations. This approach may be attractive if there is lack of time or staff within the laboratory to write the requirements specification. Expressing a personal

view, the authors consider it better to involve the analysts in preparing the specification as they will be putting the system into operation and they know their own laboratory, regardless of which approach is taken.

When considering a large LIMS one question that may be raised is that of phased implementations. This is when different parts of the system are introduced to the users at different times. Hong suggests that this is not ideal as the users will be faced with several different software systems before the final version is established. Whilst agreeing with this view, the authors would maintain that phased implementation of a LIMS is possible providing that each new phase is a complete module of the whole system and does not destroy the previous work nor change the overall operation of the system. Indeed, if the LIMS is highly customised then a phased implementation may be highly desirable.

There are two types of philosophy concerning the implementation of a LIMS. The first is a “black box” approach where all data is acquired and processed automatically by the system with little intervention from the analyst; this approach would use extensively the automatic calculations discussed in Part I. The alternative is to think of a LIMS as another analytical instrument to be used and controlled by an analyst whose responsibility is to accept or reject data or any calculations. The type of laboratory, staff available, workload and assays will determine the course of action to take.

In summary, good planning and forethought are essential to lay the basis for overall success and provide for the growth of the system in the future. If an analysis of your laboratory needs indicates a LIM system, proceed to the next section. Some laboratory managers, after this analysis, may find that they do not require a LIM system although the analysis in itself may make them more productive by highlighting inefficiencies. It should be pointed out that a LIMS will probably entail staff working with less flexibility compared with manual systems, however the benefits of such a system should outweigh this disadvantage.

Source of the LIMS

There are three ways to acquire a LIMS: (i) by in-house development; (ii) from a software house; and (iii) from a commercial supplier. The advantages and disadvantages of each source are discussed.

In-house development. If a do-it-yourself approach is adopted, whereby a computer department or other individuals develop the software to the specification, this will mean a huge resource commitment by the site. The easiest method would be to take an existing commercial database and write the requisite routines around it in order to access the information properly. The major disadvantage would be the length of time needed to write the software, together with the resources required, e.g. taking on, or redeploying staff.The advantage would be that laboratory staff have a system written specifically for their needs, although enhancement of the system could only come from within that laboratory. The huge demands of a LIMS project on computing resources make it doubtful whether any, except the largest companies would choose this route.Given the status of commercial LIMS software today, this approach seems akin to reinventing the wheel.

Software house. The choice of a software house to provide the LIMS system is a viable alternative; the end result should be exactly what you require but the development costs will be high, especially if the system is unique. The time taken to write the software will depend on the expertise of the supplier and the programming staff employed. If the software company has been well chosen they should have some expertise in this field and should be able to use or adapt existing software in this project and help keep costs down.As in the case of the in-house development, extensions to the system would come from within the laboratory and these would be chargeable if the system were not maintained in-house.

Commercial supplier. The last option is to use a commercial supplier. Over recent years analytical instrument companies have seen that information management is a

logical extension of their product ranges, so much so that all major manufacturers now offer LIMS in one form or another. These commercially available systems are competitively priced, the development costs are spread over the whole customer base and the systems are sold in competition with other vendors. Competition means the product is under continuous development and is constantly evolving as ideas are incorporated for the benefit of all users. The overall development of the package can take many tens of man years and this will increase throughout the lifetime of the product.

When assessing the standard packages from an instrument company it is important to visualise how they would operate in your own laboratory. As the operation of every laboratory tends to be different there will be a certain amount of tailoring of the standard package to your requirements. However, for specific needs, e.g. specialised reporting requirements or graphical presentation of results, custom software will need to be written. How much is required will obviously influence the final price of the system. If there is a suitable computer on site it may be possible to save on some hardware costs just by purchasing the software rather than the whole system. This has been the approach of the authors colleagues in the Quality Control Department, SK&F Laboratories, Welwyn Garden City, UK.

In choosing a commercial system, the basis of their operation must be borne in mind: most standard commercial systems are specification driven. That is, aimed towards a quality control environment in which small numbers of samples are put through relatively large numbers of tests. After splitting the original sample, ensuing results must be collated to see if they meet a predefined specification. However, the authors' application required a protocol driven system to cope with the reverse situation in that the Department receives a large number of similar, but unique, samples and usually applies a single test. Frequently, individual samples are irreplaceable and of limited volume - being biological in origin. Although individual samples are important,it is the relationship and trends between groups of samples that is sought. The concentrations to be measured result from many pharmaceutical and biological factors and they cannot be compared to any meaningful standard value. This is a vital distinction for laboratories working in the analysis of biological fluids in the pharmaceutical industry.

If a commercial vendor is to be chosen, the best advice is look closely at all the available systems, because the final choice will depend on several factors such as economics, time constraints - both for delivery of the hardware and the writing of the software, including any customisation. It is essential to visit a site that possesses such a system as one is proposing to purchase and to obtain the comments of the people who have used the system. Hong details more advice to prospective purchasers of commerical LIM systems.

Comments on the appearance of the software and how it would operate in the laboratory are relatively easy for analysts. However, appreciation of the computer operation and how the database stores and retrieves data come best from experienced computer personnel (the advice is much better if they have the laboratory experience to appreciate the problems of analysis). This experience and advice manifests itself in the sizing of the hardware: e.g. considerations of memory and disc size. In the authors' project this worked very well and the advice was always excellent.

Choice of supplier

The choice of supplier depends on a number of factors, the first of which is the ability of the supplier to meet the requirements specification with their standard system. Any potential supplier should indicate in their response what areas they cannot meet. Custom software may be a method of overcoming the problem. Furthermore, detailed discussions should ascertain whether they can fulfil the requirements in practice. All these discussions are time consuming but it is essential to evaluate the potential of each considered supplier of

a LIMS. The selection process cannot be hurried.The cost analysis justification for a LIMS has been presented by Golden although intended for an American readership it shows how a LIMS could pay for itself in two to three years.Credibility of the supplier is important. This can be established in several ways; by visiting sites where relevant systems have been installed and obtaining first-hand information concerning the advantages and problems they have had. Meeting users is another good way of finding out how a particular LIMS has developed and learning how much effort is being put into the product.The timing of delivery may be an important factor, for instance if the LIMS needs to be installed within a set time for budgetary or other reasons.The after sales support and training offered is another area of vital importance. The first 12 months after delivery is when many problems occur, particularly major problems in the software and the users' inexperience in dealing with faults are highlighted. The location of the vendor relative to the site may be an important factor. Once a LIMS has been purchased from a supplier, the user is then linked with that vendor for the life of the system. Enhancements, if not written by the users can be expensive as can software upgrades when the basic system has been extensively customised.The need to have a clear understanding of the requirements before approaching any potential supplier cannot be overstated.

Functional and systems specifications

Functional specification. Once the choice of supplier has been made the hard work begins. The requirements specification produced earlier is used as a basis for producing a further document called the functional specification which defines the functions of the system without detailing the methods by which those will be achieved.

Systems specification. Often a further systems specification is produced that defines the methods to be used to implement the required function of the LIMS. This is the specification which the programmers will use to produce the actual software for the system concerned, and will include such items as the screen layout and the procedural logic for all the tasks that the LIMS will perform.

In practice, it is unlikely that a fully working and functional LIMS can be obtained from the specification documents at the first attempt. The reasons are:
(i) It is inevitable that some functions that looked attractive on paper will prove to be difficult to use practically;
(ii) There will be areas that will be underspecified or even omitted;
(iii) Sections will be wrongly specified.

Validation of LIMS computers

Validation is probably the most neglected area of scientific computing. This is surprising, considering the impact computers have had in recent years and the fact that many industries come under external regulations. Little has been done until recently to incorporate any quality assurance requirements into computerised systems. Although the computer can provide many powerful enhancements in quality assurance for the laboratory with increased data integrity, the use of a computer does not guarantee that a given program is valid.

At this point it is useful to define some terms using the work of Chapman:
validation, establishing documented evidence that a system does what it purports to do;
validation protocol, a prospective experimental plan that, when executed, is intended to produce documented evidence that the system has been validated. The keyword in both these definitions is "documented".

Initially, validation is aided by good system design (through the various specification documents) and the software quality assurance practices of the supplier. Ideally, the LIMS should be checked thoroughly by the supplier before delivery to ensure that the system works in the manner prescribed. It is essential that the software supplier has a defined test plan and that the results of it are available to the customer. In the authors' experience, the

best personnel to validate the LIMS are scientists, because the supplier will not have intimate knowledge of the working methods of the laboratory.

Moreover, the FDA considers the final user of the system to be primarily responsible for the validation process [19]. It is therefore imperative that the analysts involved with the validation are allowed sufficient time to undertake these tasks: it is unacceptable to expect them to validate the computer and perform their normal work at the same time. How does one validate a computer system? The FDA Good Laboratory Practice Regulations (GLP), written before wide spread introduction of computers within analytical laboratories, states:

"Equipment shall be adequately inspected, cleaned and maintained. Equipment used for the generation, measurement, or assessment of data shall be adequately tested, calibrated and/or standardised."
"Written records shall be maintained of all inspection, maintenance, testing, calibration and/or standardising operations."

In this instance, the LIMS can be considered as an analytical instrument.It must be realised from the outset, that computer systems other than the simplest cannot be completely validated. Therefore errors will be discovered later during operation of the system. The US Department of Defence, for example, lays down minimum standards that 100% of the statements in any software component be executed during validation and that 85% of the possible branches be executed. Exhaustive software validation takes place in the avionics and space industries where lives depend on the validity of the software in computer controlled operations. For instance, 44% of the total software budget of Saturn V project was spent on software validation. This amount of effort is excessive in the context of analytical laboratories but does not remove the onus of validation from the user. It is necessary to restrict validation to some achievable goal that will engender an acceptable level of confidence in the system. The validation protocol is the means of achieving this. For convenience, the LIMS can be divided into two parts: the computer hardware and the software, of which the latter is further split into the operating system and software modules. Each aspect will be considered in turn.

Benefits of a LIMS

The revolution in analytical instrumentation promises high productivity providing that the analysts involved are correctly educated and trained. Once this is achieved the benefits of a LIMS can be realised.There is little in the scientific literature written by users concerning the benefits of LIMS, reflecting that these are early days in the development of this type of laboratory automation.Major benefits are realised by laboratories that have successfully installed LIMS systems. These are data storage, ease of data manipulation, and data integrity, which together produce increases in productivity. Each area will be examined in turn.

Data storage

Data storage is the fundamental basis from which all other benefits of LIMS are based. The database facilities searching of on-line analytical data; thus, efficient sample tracking to ascertain the status of a particular analysis is easily accomplished. Additionally,previous results can be searched on-line, this is very useful when compiling year-end figures for a particular project or reporting results.

Data integrity

Compliance with regulatory agency guidelines is crucial to the acceptance of studies supporting the registration of a new drug or agrochemical. Here LIMS can be of great value. All changes to the database are monitored by the audit trail which ensures that any modification is recorded. Furthermore, the use of validated programs ensures adherence to any procedures laid down in the relevant SOP. Although the benefits in this area are difficult to quantify, their importance should not be understated. As the majority of scientists

appreciate, the checking of analytical data is a very tedious task where mistakes are easily made. The benefit of computerisation will be to avoid transcription checking.
Verification of data entry, using either cross-reference to datasets or via bar codes, is a very powerful method of ensuring data integrity, as well as building confidence in the system and the results produced. Automatic calculations can also be performed to avoid repetitive calculations and transcription errors through manual data entry.

Data manipulation

Data manipulation allows the user to transform data into information efficiently and without error. For example automatic calculation, collation and reporting of results are areas where LIMS excels. When using validated computer programs the required information can be extracted from the database and rapidly included in reports.The acceptance and validation of large numbers of plasma samples from clinical and preclinical studies in drug development can cause long delays before the emergence of the final report. In the authors' laboratories this process was speeded up by plotting each set of subject samples on the screen together with the calibrated curve, if required.Moreover, to aid the process, colour was used to display the data and make interpretation easier.This facility displays the calibrated curve in the form of a graph of the drug/internal standard ratio versus drug concentration with the slope,intercept, correlation coefficient of the line calculated from a regression. A prompt asks the analyst if all the points are acceptable, if not a table showing the individual points is displayed and the operator can change the status of any standard to "unacceptable". If this is done, when the graph is next displayed the unacceptable point is shown in a different colour and symbol; note that any points deemed unacceptable cannot be removed from the display and indeed they can be reinstated during this process if required. With each new display the intercept, correlation coefficient etc. are recalculated and shown on the sideof the screen. When it is acceptable the calibrated curve is then used to calculate the concentration of drug in the subject samples.

Productivity

Productivity increases will be dependent on the aims and configuration of the system, however, it is an area where the gains from manipulation, integrity and storage of data are apparent.No definitive study has been performed to assess the overall benefits of LIMS. Increases in productivity of 10-20% is the average estimate made by most laboratory managers who have installed such systems. A similar figure is given by Golden who assessed the impact of LIMS in both R&D and QC environments. In the former instance, increases in productivity are the main benefit by removing the transcription and checking of data brought about by automatic data capture. This productivity is manifested by the speed at which a product can be perfected and brought to the market place. The rationale for LIMS here is not only the improvement in productivity or in the speed at which specific analyses are completed but lies in the laboratories' ability to complete entire projects quicker.LIMS in a QC environment has the ability to quickly accept or reject raw material lots or manufactured goods, thus smaller raw material stocks can be held and finished goods marketed quicker. These are areas of benefit in addition to the increases in productivity.The use of bar coded labels generated from the authors' system has saved staff in many departments from writing the labels by hand, enabling us to have uniformally labelled tubes and a speedy method for data entry into the computer.An aspect of LIMS included the integration of the system with word processing,this can be achieved by installing a word processing package within LIMS. The LIMS can generate reports in predefined formats by writing data files to disc.

TEXT INFORMATION MANAGEMENT SYSTEM (TIMS)

The name 'TIMS' is not as widely used as the name 'LIMS'. Nevertheless text information management system is essential in preclinical development because huge number of text documents and other related information such as images, drawings and photographs are generated in the area. All these information are considered intellectual property and require

protection and easy access. One of the characteristics of the pharamaceutical industry is large quantities of paperwork, particularly in areas where GMP/GLP are strictly enforced. The scientists in preclinical development spent quite a large percentage of their working time writing compound documents(reports). The report generation, review, approval, filling and retrieval process will be very inefficient and even bureaucratic in a pharamaceutical company partly because of the strict regulations. The following scenario could be seen often as recently as the late 1980s. The scientist could prepare his report with one type or another of text and graphic software often through multiple cut and paste procedures to include pictures and images. Then scientist could make hard copies of the report for review by the managers and department head. After all the corrections were made it goes for auditing to QA auditor. It could take months before the report was finally ready to be filed in the company record center, where photocopies and microfilms were made and indexing took place. When an end user needed a copy of the report, he would have to make a request to the record center for a copy.

When TIMS is used in today's workflow the scientist can use a report template to facilitate report writing to include data and figures. After the draft report is completed, the scientist can send to the reviewers an electronic link of the document. The reviewers can review the document and make changes and corrections with the tracking change function. When the review is completed, the author can choose to accept the changes or deny them. If auditing is needed the same process can be used. The finalized document is issued within the TIMS by adding an issue date and signatures, if necessary converting into an unalterable file. Future changes made after issuance are captured through version control. End users can also access the issued document electronically and remotely. Comparison of the new process vs old one has demonstrated the advantages of TIMS.

Requirements in preclinical development

In preclinical development the GMP/GLP regulations are enforced not only for scientific data but also for text documents. Most of the documents are managed by the fully validated TIMS. These are important documents and they evolve along with development phases. Drug substances and products for trials are tested based on these documents, and so are the stability samples. It is critical to ensure that analyst will perform right tests against the right specifications with the correct version of the test method. Therefore a mechanism must be in place to control these documents. This can be done manually or with TIMS. A manually controlled system would require the analyst to sign out hard copies of the documents from a central location. After the testing is done, the analyst would have to return these controlled documents to the central location. Sometimes mistakes can be made with regard to the correct documents, and this will result in repetition and unnecessary investigation. If TIMS is implemented the analyst can obtain the documents from the secured database and the documents should be destroyed after the test is completed.

Standard Operating Procedures (SOP):- The SOPs are controlled in away similar to that of specification documents and analytical methods. It must be ensured that the correct versions of the SOPs are accessed and used by the scientists. After use, the hard copies should be destroyed and disposed of properly. An added requirement in that the SOPs should be accessible during working hours without interruption. Hard copies should be available at a manageable location so that the SOPs are available when the electronic system is down.

Research reports:- Research reports such as stability reports, method validation and transfer reports and pharamaceutical development reports are key documents used for NDA/MAA fillings. These documents are strictly version control.

Laboratory notebooks:- It may be debatable o consider laboratory notebooks as text documents but they should be mentioned here because of their importance in preclinical development. Laboratory notebooks are used to record experimental procedures, observations, raw data and other important information. Although laboratory notebooks are rarely used for submission to regulatory agencies directly are available for inspection by the authorities in the preapproval but still most of the pharmaceutical companies using paper based laboratory notebooks.

Current TIMS products:

Various so called Enterprise Content Management (ECM) systems are commercially available that can meet different end user requirements. TIMS used in preclinical text document management usually is a simplified version of ECM. At the highest enterprise platform level ECM vendors include documentum, file net, interwoven, stellent and vignette. At a lower level, the upper tier products are provided by day software, fat wire and IBM. For less costly products there are ingeniux, paper thin, red dot solutions and serena software. It should also be pointed out that the cost of acquiring and maintaining a fully validated TIMS is much higher than that of a non-GMP/GLP system. Therefore many of the non-GMP/GLP documents in early phase development are managed with non-validated TIMS.