Computer as data analysis in Preclinical development

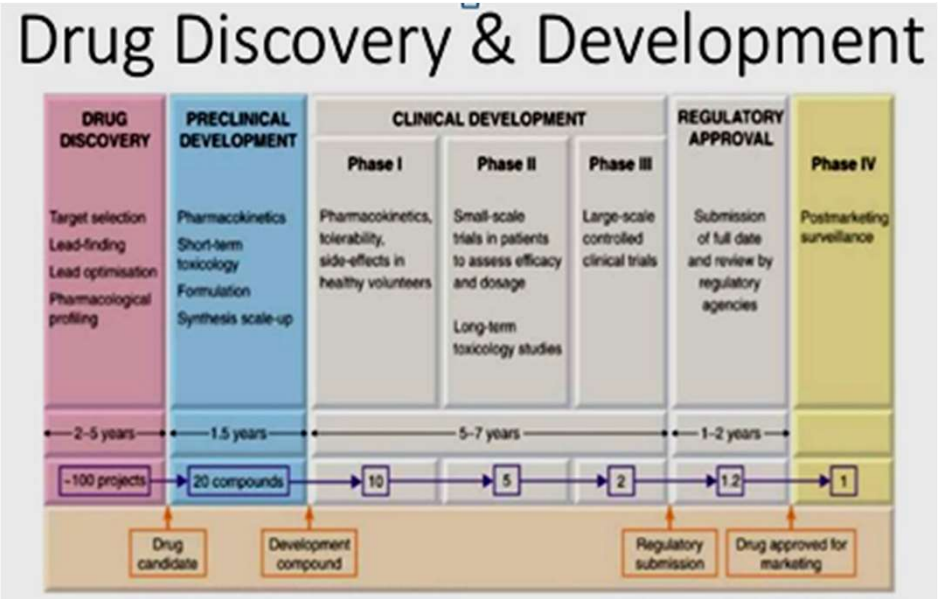
Preclinical Development

➢In drug development, preclinical development, also named preclinical studies and nonclinical studies, is a stage of research that begins before clinical trials (testing in humans) can begin, and during which important feasibility, iterative testing and drug safety data are collected.

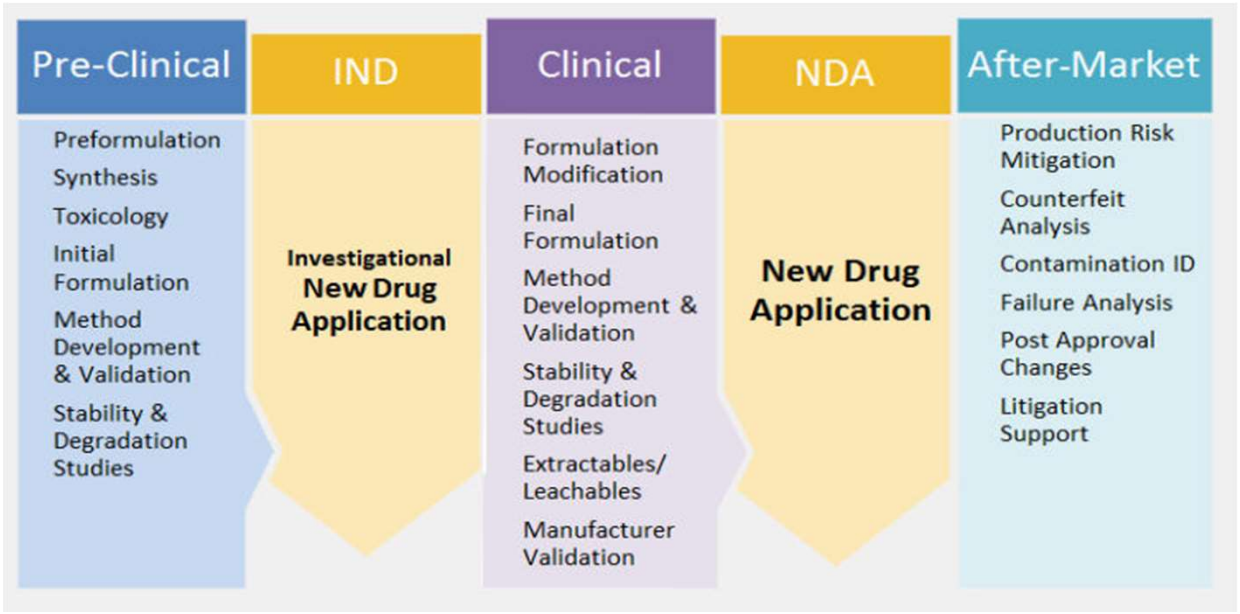
➢The main goals of pre-clinical studies are to determine the safe dose for first-in-man study and assess a product's safety profile.

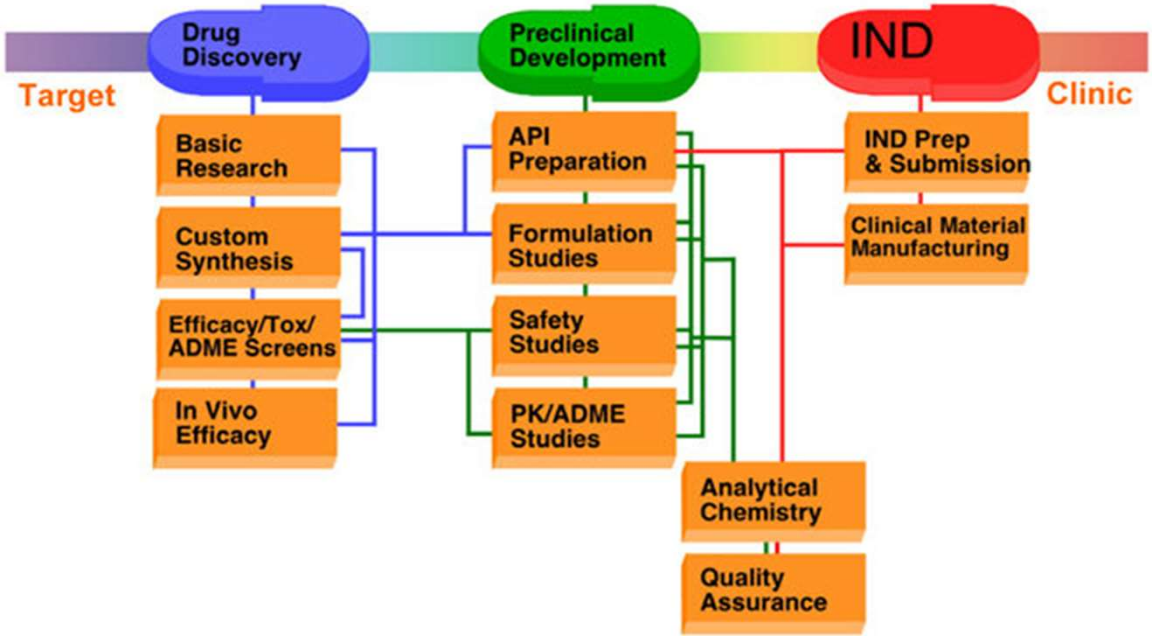
➢Preclinical studies are conducted to define pharmacological and toxicological effects not only prior to initiation of human studies but throughout clinical development.

➢Both in vitro and in vivo studies can contribute to this characterization.



Preclinical Data in Drug Development





Introduction

- Scientists from many different disciplines participate in pharmaceutical development.

- Their research areas may be very different, but they all generate scientific data (and text documents), which are the products of development laboratories.

- Literally, truckloads of data and documents are submitted to the regulatory authorities in support of investigational and marketing authorization filings.

- For example, even a typical Investigational New Drug (IND) application requires around 50,000 pages of supporting documents.

- One way or another, every single data point has to go through the acquiring, analyzing, managing, reporting, auditing, and archiving process according to a set of specific rules and regulations.

- Needless to say, the wide use of computers has tremendously increased efficiency and productivity in pharmaceutical development.

Introduction

- This overview discusses these topics briefly by focusing on the preclinical development area (also known as the area of Chemical Manufacturing and Control, or CMC).

- Considering the pervasiveness of computer applications in every scientist's daily activities, special emphases are put on three widely used computer systems:

- CDS—chromatographic data systems
- LIMS—laboratory information management systems
- TIMS—text information management systems

- These three computer systems handle the majority of the work in data/document management in the preclinical area, supporting the New Drug Application (NDA) and Marketing Authorization Application(MAA) filings.

The following are examples of the development activities that generate the majority of the data:

- Drug substance/drug product purity, potency, and other testing
- Drug substance/drug product stability testing
- Method development, validation, and transfer
- Drug product formulation development
- Drug substance/drug product manufacturing process development, validation and transfer
- Master production and control record keeping(MPCR)
- Batch production and control record keeping (BPCR)
- Equipment cleaning testing

CHROMATOGRAPHIC DATA SYSTEMS (CDS)

- The importance of CDS is directly related to the roles that chromatography, particularly high-performance liquid chromatography (HPLC) and gas chromatography(GC), play in pharmaceutical analysis.

- HPLC and GC are the main workhorses in pharmaceutical analysis.

- In today's pharmaceutical companies, development work cannot be done without HPLC and GC.

- CDS are also used for several other instrumental analysis technologies such as ion (exchange) chromatography (IC), capillary electrophoresis (CE), and supercritical fluid chromatography (SFC).

The Days Before CDS

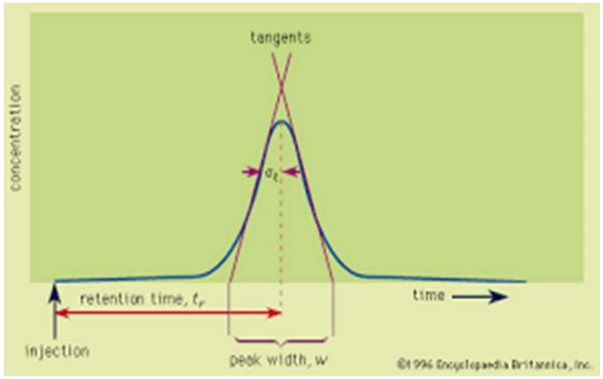
➢In the 1960s and early 1970s, chromatographs were relatively primitive and inefficient. Chromatographers had to use micro syringes for sample injection and stopwatches for measurement of retention times.

➢The chromatograms were collected with a strip chart recorder.

➢Data analysis was also performed manually.

➢Peak areas were obtained by drawing a "best fit" triangle manually for each peak and then using the equation Area = ½Base × Height.

➢At that time, the management of chromatographic data was essentially paper based and very inefficient



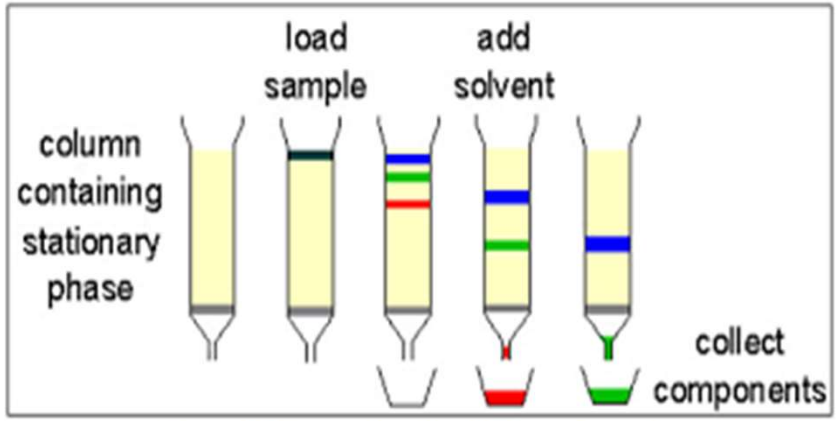


Figure 3.14 principle of liquid chromatography

The Days Before CDS

- Compared with the traditional analytical methods, the adoption of chromatographic methods represented a significant improvement in pharmaceutical analysis.

- This was because chromatographic methods had the advantages of method specificity, the ability to separate and detect low-level impurities.

- Specificity is especially important for methods intended for early phase drug development when the chemical and physical properties of the active pharmaceutical ingredient (API) are not fully understood and the synthetic processes are not fully developed.

- Therefore the assurance of safety in clinical trials of an API relies heavily on the ability of analytical methods to detect and quantitate unknown impurities that may pose safety concerns.

The Days Before CDS

- In the mid-1970s, the integrator was introduced.
- At first, the integrator worked similarly to a strip chart recorder with the added capabilities of automatically calculating peak area and peak height.
- Because of limited available memory, chromatograms could not be stored for batch processing.
- However, new models with increasing capabilities quickly replaced the older ones.
- The newer models had a battery back-up to maintain integration parameters and larger memory modules to allow the storage of chromatograms for playback and reintegration.
- At that time, the integrator increased productivity and efficiency in pharmaceutical analysis, which in turn made HPLC and GC even more popular.

The Emergence and Evolution of CDS

- The first generation of CDS systems were based on a working model of multiuser, time-sharing minicomputers.
- The minicomputers were connected to terminals in the laboratory that the analysts would use.
- The detector channels of the chromatographs were connected to the data system through a device called the analog-to-digital.
- (A/D) converter, which would convert the analog signals from the detectors into digital signals.
- In the late 1970s, Hewlett-Packard introduced the HP-3300 series data-acquisition system.
- Through the A/D converters, the HP system was able to collect chromatographic data from up to 60 detector channels.
- This represented the beginning of computerized chromatographic data analysis and management
- Because the CDS used a dedicated hardware and wiring system, it was relatively expensive to install.

The Modern CDS

- Use of server-based computing is only one of the important features of the modern CDS.
- The other two important features are the use of embedded data structure and direct instrument control.
- The earlier generations of CDS used a directory file structure, meaning that the raw data and other files such as the instrument method and data processing method were stored at separate locations.
- The most significant drawback of this type of file management was the potential for methods and raw data to be accidentally overwritten.
- To prevent this from happening, the raw data and result files must be locked. If in some cases the locked data needed to be reprocessed, the system administrator must unlock the files.
- The embedded relational database has been widely used for LIMS and is a much better file structure.
- The embedded data structure can be used to manage not only chromatographic data, but also all aspects of the CDS, including system security and user privileges.
- The embedded data structure maintains all information and changes by date- and time stamping them to prevent accidental overwriting of raw data and method files.
- It controls versions of all processed result files, acquisition methods, processing methods, and reporting methods to provide full audit trails.
- All data (acquisition, process, and reporting methods) related to a specific result are tied together.

The Modern CDS

- Direct instrument control (or the lack of it) was an important issue for the earlier version of CDS.
- The scheme of connecting the detector channels through A/Ds to CDS worked well in analytical laboratories across the pharmaceutical industry.
- The scheme provided enough flexibility so that the CDS could collect data from a variety of instruments, including GC, HPLC, IC,SFC, and CE.
- It was equally important that the CDS could be connected to instruments that were manufactured by different vendors.
- It could not be guaranteed that the proper instrument parameters were used in sample analysis.
- Another need came from the increased use of information-rich detectors such as photodiode array detectors and mass spectrometer(MS) detectors.
- The data from these detectors could not be collected by CDS through A/Ds.
- This represented an important gap in reaching full compliance of the 21 CFR Part 11 regulations.
- Direct instrument control would avoid these problems.
- To address these problems, the instrument vendors had to cooperate by providing each other with the source codes of their software. Some progress has been made in this area.
- A good example is that of the CDS Empower (Waters), which now can directly control HPLC and GC equipment manufactured by Agilent.

Lists of the major CDS vendors and current contact information.

Major CDS Vendors and Their Products

Product	Vendor	URL
Atlas	Thermo Electron Co.	www.thermolabsystems.com
Cerity	Agilent Technologies, Inc.	www.agilent.com
Chromeleon	Dionex Co.	www.dionex.com
Class VP	Shimadzu Scientific Inst.	www.shimadzu.com
Empower	Waters Co	www.waters.com
EZChrom Elite	Scientific Software, Inc	www.scisw.com
Galaxie	Varian Inc.	www.varianinc.com
TotalChrom	Perkin-Elmer, Inc.	www.perkinelmer.com

Summary

- CDS have helped the pharmaceutical industry to increase efficiency and productivity by automating a large part of pharmaceutical analysis.

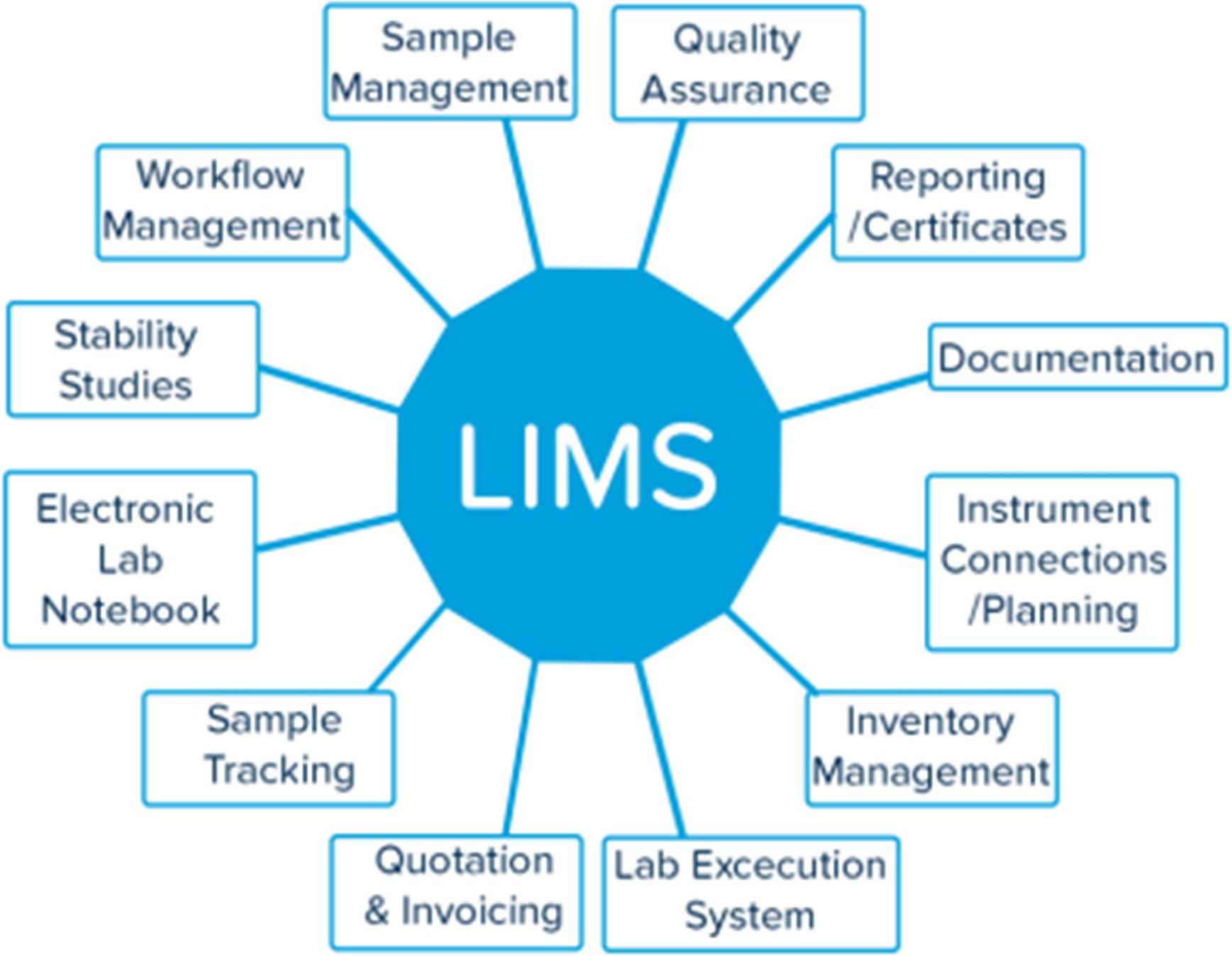
- So far the main focus of CDS has been on providing accurate and reliable data.

- The current regulatory trend in the pharmaceutical industry is to shift from data-based filings to information-based filings, meaning that the data must be analyzed and converted into information.

- This implies that enhancements in data searching and trend analysis capabilities will be desirable in the future.

Laboratory Information Management Systems (LIMS)

- Laboratory information management systems, or LIMS represent an integral part of the data management systems used in preclinical development.
- LIMS are needed partly because CDS cannot provide enough data management capability.
- For example, CDS cannot handle data from nonchromatographic tests.
- Another important use of LIMS is for sample management in preclinical development, more specifically in drug substance and drug product stability studies.
- Stability studies are very labor intensive, LIMS are designed to automate a large part of these stability studies including sample tracking, sample distribution, work assignment, results capturing, data processing, data review and approval, report generation, and data archiving, retrieving, and sharing.


LIMS
Sample Management
Quality Assurance
Reporting /Certificates
Documentation
Instrument Connections /Planning
Inventory Management
Lab Excecution System
Quotation & Invoicing
Sample Tracking
Electronic Lab Notebook
Stability Studies
Workflow Management

Component of LIMS

LIMS has more core functinalities in managing laboratory data and other electronic information

1.Software-is set of instructions to be carried out by physical hardware components. It dectate how and which information is stored in data base, how calculations are performed and how information is displayed on the terminal.

2. Cables physical component, provide pathway of movement of data and control signal to and from various devices.

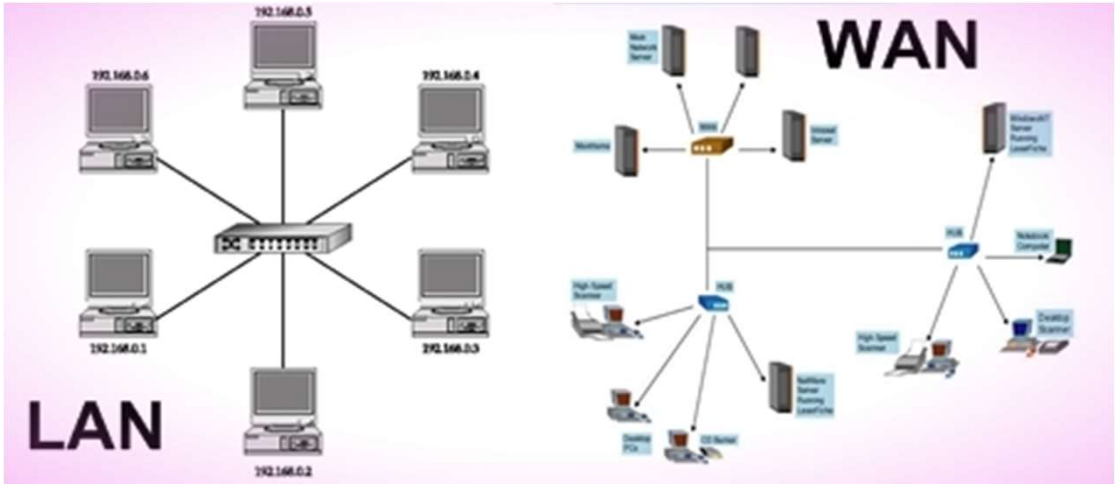
3.Networking Hardware- ties several computer together . They includes specialized high speed switches , protocol translators. Network require sophisticated web of specialized hardware. network management software and communication lines. Interface establishes data connectivity between instrument and computer.

4. Operating system provides control of basic function of computer and co-ordination of physical hardware

Four Types of Architectural Options When Implementing LIMS

1.LAN (local area network) installation. In a multiple site situation and through the standard client/server setup, the application would be hosted separately on a server at each site connected to PC clients. In this setup, the LIMS are installed on both the clients and the server. System administration is required at each facility.

2.WAN (wide area network) installation- In this setup the LIMS take advantage of telecommunication technology to cover a great distance. The setup can also be used to connect disparate LANs together. In this configuration, the LIMS are installed on both the clients and a central server.



3.Centrally hosted thin client installation-

For this setup, system administration is managed at a corporate center, where the LIMS are hosted and distributed via a WAN or the Internet with a virtual private network (VPN).

4.ASP (Application Service Provision provider)-hosted installation.-

In this setup, the LIMS are hosted on a centrally managed server form and maintained by third-party specialists. Users access the LIMS with any Internet-connected PC with a standard Web browser.

LIMS Vendors Specialized in Pharmaceutical Industry

Product	Vendor	URL
Debra	LabLogic Systems Ltd	www.lablogic.com
Q-DIS/QM	Waters	www.waters.com
QC Client	Agilent	www.agilent.com
WinLIMS	QSI	www.lims-software.com
ACD/SLIMS	Advanced Chemistry Development	www.acdlabs.com
V-LIMS	Advance Technology Corp	www.vetstar.com
VET/HEX	HEX Laboratory Systems	www.hexlab.com
BioLIMS	PE Informatics	www.pebiosystems.com
LabCat	Innovative Programming Assoc.	www.labcat.com

Advantages of LIMS

1. Efficiency: LIMS streamlines data entry by automating the process.This results in less time, faster access to data and accurate up-to date data.

2. Cost Reduction –cost of labor, resources etc are reduced by using LIMS.

3. Compliance –LIMS assist in real-time monitoring and quality control. Work flows can be managed , sample logged and tests can be checked against protocol and procedure to ensure compliance.

Thank You