Name of Unit	Computer as data analysis in Preclinical development
Course/Subject Name	Computer Application in Pharmacy
Course/Subject Code	BP205T
Semester	II
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Learning Outcome of Modules 05

LO	**Learning Outcome**	**Course Outcome Code**
LO1	To understand different types of databases, applications of computers and databases in pharmacy.	BP205.5
LO2	To illustrate the concept of Number system in computer.	BP205.5
LO3	To make use of web technologies such as HTML, XML, CSS, Programming languages, web servers and pharmacy drug database.	BP205.5
LO4	To appraise the applications of computers in pharmacy such as drug information services, pharmacokinetics, mathematical model in drug design, hospital and clinical pharmacy.	BP205.5
LO5	To explain about bioinformatics and its impact in vaccine discovery. To elaborate the applications of computers for data analysis in preclinical development.	BP205.5

Content Table

Topic
• Role of computer in preclinical development. • Chromatographic Data Analysis. • LIMS and TIMS.

COMPUTER AS DATA ANALYSIS IN PRECLINICAL 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.

On the other hand, it has also created unique problems and challenges for the industry. 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, pecial emphases are puton three widely used computer systems:

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

It may also be beneficial to the reader if we define the sources of the scientific data in preclinical development. Some development activities that generate the majority of the data are:

- 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, andtransfer
- Master production and control record keeping
- Batch production and control record keeping
- 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 Emergence and Evolution of CDS

For some instrument vendors, the early CDS were developed as proprietary products to help with the sale of instruments. 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

Drawbacks of CDS

- Because the CDS used a dedicated hardware and wiring system, it was relatively expensive to install.
- Difficult to scale up because more minicomputers would be needed with increases in the number of users.

- The performance of the system would degrade as the number of usersincreased.

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. There would either be no connections or only partial connections between these files. 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 of the metadata (acquisition, process, and reporting methods) related to a specific result are tied together

Laboratory Information Management Systems

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, and the results have an important impact on regulatory filings. 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 Hardware and Architectures

Commercial LIMS appeared on the market in the early 1980s. These operated on then state-of-the-art minicomputers such as the 16-bit Hewlett-Packard 1000 and 32-bitDigital VAX system. By the late 1980s, several DOS-based PC LIMS operating on the primitive PC network were available.

By the early 1990s, most LIMS started using commercial relational database technology and client/server systems, which operated on UNIX or the new Windows NT platform. The most advanced LIMS utilize server-based architecture to ensure system security and control.

There are four main types of architectural options when implementing LIMS. The first is the LAN (local area network) installation. In a multiplesite 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.

The second type is the 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. The third type is the so-called “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 WANor the Internet with a virtual private network (VPN). The last and also the newest type is the 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.

Different Types of LIMS

The implementation of LIMS requires a significant amount of investment in capital money and manpower. There are large numbers of established vendors that provide commercial LIMS with a similar range of core functionality, but few of them are dedicated to the pharmaceutical industry because of the market size . The following discussion is not intended to categorize different types of LIMS; rather, we briefly point out the most obvious characteristics of different LIMS. LIMS may possess certain distinctive features, but their core functionalities may be very similar.

Customer-tailored LIMS

In an implementation of this type of LIMS, the customer purchases a generic product from the vendor. The vendor and customer will work together over a period of time to configure the software to adapt it to meet end user needs. This usually involves extensive programming, which can be performed by the trained end user or dedicated supporting personnel on the customer side. Programming support is usually needed for the entire life of the LIMS to accommodate changes in development projects. The advantage is that the LIMS functions relatively closely to the business practices of the customer and the system can be tailored to fit the needs of the customer's development projects. The disadvantage is that it takes considerable resources to implement and maintain the LIMS.

Preconfigured LIMS

This LIMS does not require extensive customer programming. To meet specific needs of end users, the vendors provide a comprehensive suite of configuration tools. These tools allow end users to add new screens, menus, functions, and reports in a rapid and intuitive manner. The tools also allow the LIMS to be more easily integrated with other business applications such as document processing, spreadsheets, and manufacturing systems.

Specialized LIMS

This type of LIMS is based on the fact that certain laboratories have a range of well-defined processes (e.g., stability testing) that are performed according to a specific set of regulations and by using well established tests. The tests are done according to industry-wide accepted protocols. Specialized LIMS are tailor made for certain types of laboratories. Therefore the performance can be optimized for clearly defined work process.

LIMS as rented service

The application service provision provider (ASP) is a means of obtaining access to software applications without the need to acquire expensive licenses and hardware or employ high-cost support resources. The application is hosted on a third-party site with system maintenance, backup, and recovery provided by a third party. Products and services can be rented for a contract period on a fixed cost per user/per month basis. The advantages of obtaining LIMS in this fashion include reduced cost in initial investment and reduced requirement of resources for maintaining the LIMS. The continued security and integrity of the data transferred over the Internet is a major concern for this type of LIMS.

TEXT INFORMATION MANAGEMENT SYSTEMS (TIMS)

The name “text information management system” is not as widely used as the name “laboratory information management system.” Nevertheless, a text document management system is essential in preclinical development because huge numbers of text documents and other related information such as images, drawings, and photographs are generated in the area. All these documents and information are considered intellectual property and require protection and easy access.

One of the characteristics of the pharmaceutical industry is large quantities of paperwork, particularly in areas where GMP/GLP are strictly enforced. The slogan “documentation, documentation, and documentation . . .” is always in the mind of laboratory scientists.

The scientists in preclinical development spend quite a large percentage of their working time writing compound documents (reports). The report generation, review, approval, filing, and retrieval process can be very inefficient or even bureaucratic in a pharmaceutical company, partly because of the strict regulations. The following scenario could be seen often as recently as the late 1980s: The scientist would prepare his report with one type or another of text and graphic software, often through multiple cut-and-paste procedures to include pictures or images. Then the scientist would make hard copies of the report for review by managers and the department head. After all the corrections were made, the scientist would print out another copy for the QA auditor for auditing (this is only done for the documents used for submission). 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 ahard copy. When TIMS is used in today's workflow, the scientist can use a report template to facilitate report writing. Some cut-and-paste procedures are still needed to include data and figures. After the draft report is completed, the scientist can send the reviewers an electronic link for 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, and converting into an unalterable PDF 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. the old one has demonstrated the advantages of TIMS.

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, FileNet, Interwoven, Stellent, and Vignette. At a lower level, the upper-tier products are provided by Day Software, FatWire, and IBM. For less costly products, there are Ingeniux, PaperThin, RedDot 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.

BENEFITS OF TIMS

- Saves time and energy
- Faster method of report generation.
- Ensures accuracy
- Improves efficiency in managingcritical data
- Reduced paper work
- Strict security
- Smooth and easy work flow

Multiple Choice Questions (2marks)

1. Preclinical studies are carried out to determine----------

a. Usage of upcoming drug
b. Safe dose of upcoming drug
c. First safe dose of upcoming drug
d. Safety of upcoming drug

Ans c

2. What is the role of computers in preclinical development?

a. Ensures management of programs
b. Acts as storehouse of information
c. Reviews computer programming techniques used in development
d. Used by pharmacists

Ans b

3. Animations and videos are a type of ------------------------- programs.

a. Computer
b. Database
c. Visual
d. Multimedia

Ans d

4. Chromatographic data analysis is related to effective workflow with in a --------

a. Drug store

b. Clinic

c. Laboratory

d.Hospital

Ans c

5. Which of the following products is used to simplify lab workflow with a unifiedcontrol for effective data management?

a. Lab information management system

b. Scientific data management system

c. Integrated solutions

d. Chromeleon 7.2 CDS Software

Ans d

6. LIMS has fastened the process of management in ------------------------ development

a. Clinical development

b. Preclinical development

c. Lab development

d. Database development

Ans b

7. Sample management is done with the help of--------------------

a. Integrated solutions

b. Scientific Data Management Systems

c. Database Management

d. Lab information management Systems

Ans d

8. Lab Inventory Management refer to -------------------

a. Lab admin

b. Lab orders

c. Lab reports

d. All of the above

Ans d

9. Text information management system is based on--------------

a. Search Queries

b. Select Queries

c. Both

d. None of the above

Ans c

10. TIMS helps in publishing ---------------------------- reports in one go.

a. Lab

b. Clinical

c. Pharmaceutical

d. Managerial

Ans c

Short Answer Questions (5 marks)

1. Discuss the role of computer in preclinical development.

2. What do you understand by the term Chromatographic Data Analysis(CDS)?

3 What are the benefits of the LIMS?

4. Explain the benefits of TIMS.

5. Write a short note on CDS products.

Long Answer Questions (10 Marks)

1. Discuss Laboratory Information Management System (LIMS) in detail.

2. Explain Text Information System and its benefits.

3. Describe Chromatographic Data Analysis and its importance.