Unit - V

Computer as data analysis in Preclinical development

Brief Notes

Scientists from many different disciplines participate in pharmaceutical development.Their esearch areas may be very different, but they all generate scientific data (and text documents), which are the products of development laboratories.

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.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, and transfer

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. HPLC, GC and CDS are used for several instrumental analysis technologies.

On 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 earlyphase 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. And, slowly, HPLC and GC established their places as the mainstream analytical methods in pharmaceutical analysis.

The more and more importantance chromatographic methods, practical needs prompted instrument vendors to come up with more efficient ways for collecting and processing chromatographic data.

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 users increased.

As instrumental analysis played an increasingly important part in pharmaceutical development, an ever-larger percentage of the data in Good Manufacturing Practice and/or Good Laboratory Practice (GMP/GLP) studies were captured and stored electronically.

With server-based computing, the applications are deployed, managed, supported, and executed on a dedicated application server. Server-based computing uses a multiuser operating system and a method for distributing the presentation of an application's interface to a client device. There are no software components installed on the client PC. The client's PC simply acts as the application server's display. CDS using this model significantly reduced the total cost in implementation and maintenance and significantly increased its compliance with regulatory guidelines.

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.

Summary:

CDS have certainly served the pharmaceutical industry well by being continuously improved. CDS have helped the pharmaceutical industry to increase efficiency and productivity by automating a large part of pharmaceutical analysis. But CDS still have room for improvement. 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 indata searching and trend analysis capabilities will be desirable in the future.

LABORATORY INFORMATION MANAGEMENT SYSTEMS (LIMS)

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. LIMS is for sample management in preclinical development, more specifically in drug substance and drug product stability studies. 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

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 **LAN (local area network)** installation. 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.

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 WAN or 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.

Different Types of LIMS:

Customer-tailored 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.

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 wellestablished 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.

Summary

LIMS is a complex system and requires significant capital and manpower investment. Selection of the right LIMS product is a daunting task, and the outcome can have a significant impact on the business.

Compared with CDS, LIMS has more core functionalities in managing laboratory data and other electronic information. It also has much stronger search and reporting capabilities. It is interesting to point out that some LIMS vendors have started to use the term “data mining” in their product introduction brochures. This means that they are aware of a new trend in the pharmaceutical industry, especially in preclinical development, namely, toward a better understanding and control of data in pharmaceutical manufacturing. The FDA has issued a new Guidance on Process Analytical Technologies (PAT), promoting the concepts of “quality by design,” “process understanding,” and “real-time assurance of quality.” These concepts may have a profound impact on how pharmaceutical development is

conducted in the future. To put these concepts into practice will mean an explosion in the amount of scientific data, not only through standard testing such as HPLCand GC but also through nonstandard technologies such as near-infrared spectroscopy, Raman spectroscopy, various particle size analysis techniques, etc. More importantly, the data will need to be analyzed with new (e.g., chemometrics) tools to generate process/product information and knowledge. The current LIMS are not designed to handle large amounts of spectral data. We will have to see whether the core functionalities of LIMS can be expanded or totally new information management systems will have to be developed to meet the new challenges.

TEXT INFORMATION MANAGEMENT SYSTEMS (TIMS)

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.

Documentation Requirements in Preclinical Development:

Product specification documents and analytical test methods—Drug substances and products for clinical trials are tested based on these documents, and so are the stability samples. A manually controlled system would require the analyst to sign out hard copies of the documents from a central location. If TIMS is implemented, the

analyst can obtain the documents from the secured database and then the documents should be destroyed after the test is completed.

Standard operating procedures (SOPs)—The SOPs are controlled in a way 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.

Research reports—Research reports such as stability reports, method validation and transfer reports, and pharmaceutical development reports are key documents used for NDA/MAA filings.

Laboratory notebooks—Laboratory notebooks are used to record experimental procedures, observations, raw data, and other important information.

Current TIMS Products:

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 nonvalidated TIMS.

Summary:

TIMS has helped the pharmaceutical industry to improve efficiency in managing business-critical text documents. However, it is still a time-consuming process to write, review, audit, approve, and publish text documents for submission. The pharmaceutical industry is working toward making submissions electronically. However, this may take time, and the industry may need many changes in business practices to reach the goal.