Trade Science Inc.

June 2009 *Volume 8 Issue 2*

Analytical CHEMISTRY
An Indian Journal
Review

ACAIJ, 8(2) 2009 [293-298]

Electronic laboratory notebooks: An evolutionary change to pharmaceutical industry

Mitesh Phale*, Dipti Korgaonkar
Department of Pharmaceutical Analysis, Prin. K.M.Kundnani College of Pharmacy,
Jote Joy Building, Rambhau Salgaonkar Marg, Cuffe Parade, Colaba, Mumbai-400005, (INDIA)
Tel : +91-9892622477; Fax : + 91-2222165282
E-mail : phalemitesh@gmail.com
Received: 26th April, 2009 ; Accepted: 1st May, 2009

ABSTRACT

Computer forms an important part of technology to increase the efficiency and quality of work in pharmaceutical industry. Regulatory authorities recognize the laboratory notebooks as the primary evidence for the patent claim. Electronic Laboratory Notebooks (ELNs) are the state of the art technique for collaborative research in science. With the wide applications of ELN, today it has laid the foundation in pharmaceutical companies. The authenticity and reliability of the records maintained with ELN, and also its regulatory acceptance make it advantageous over the traditional methods of record keeping in pharmaceutical companies. The ELN technology with its advantages distinctly outweighs the disadvantages and risk associated with the changes in record keeping procedures. Thus the adoption of electronic media for record keeping is not a revolutionary change, but an evolutionary process which will have a wider acceptance in the coming future.

KEYWORDS

Electronic laboratory notebook;
ELN;
Documentation.

INTRODUCTION

Today the traditional R and D in pharmaceutical companies has come to a break down, which has accelerated the drug discovery and development process. But this has also led to an increased need for robust communications and data-sharing mechanisms. Documentation forms an integral part of R&D, as documenting an experiment in a way to ensure that the record can act as evidence to support a patent claim or to demonstrate compliances with the US Food and Drug Administration's (FDA's) predicate rules, puts demands on an electronic laboratory notebook (ELN) that are not trivial. The commonly used paper laboratory notebooks are slowly becoming obsolete, as the needs of scientist for recording the scientific data are no longer met.

The 'first to file' a patent application was termed as a winner initially, but today the focus has changed with the new law in United States i.e. 'first to invent' has the right to obtain patent protection for an invention. Thus lab notebooks form a vital part of any research project. The electronic laboratory notebooks, or ELNs, systems offer secure version control and audit trails to capture the flow of the scientific process, promote collaboration among scientists, and help protect intellectual property assets.

Thus the increasing acceptance of electronic records by the FDA, with limitations of paper notebooks have given rise to development of innovative software programs that allow scientists to create electronic records that efficiently capture and store data and supporting information[1-3].

Data management system

Data generated from any experiments should be documented in a way that it ensures that the record can

be used to support a patent claim or compliance with the guidelines. The vital aspect of any research work is maintenance of accurate records of the experiments performed. Not only has the laboratory notebook formed a prominent official record of the observations of the experiments but also it helps the scientist to keep track of their experimental ideas. From the researcher's point of view the laboratory notebook can be very helpful for years, if he maintains it properly. But for scientific organization, lab notebooks are a blend of knowledge and experience. Electronic laboratory notebook (ELN) is the state of the art technique for collaborative research in science, especially if the project involves a large quantity of data[4,5].

Laboratory notebook

Laboratory notebooks represent the entire work flow of the research and development (R&D). The main role played by laboratory notebook is recording of work that was done so that research can be repeated, or avoided if the outcome was not the desired outcome, and to allow subsequent research to move forward based on previous results. Traditionally, the laboratory notebook medium is paper and data entries are handwritten. This medium is portable, easy to use, well understood by users, and, with a little care, a durable method of recording[2].

Paper laboratory notebook management

The scientific community consists of paper notebooks which are ubiquitous. Researchers keep personal notebooks to record their ideas, meetings, and experiments. The observations and ideas expressed in these notebooks are usually not disclosed unless needed to prove when an idea was first recorded, in case of patent claims. Notebooks are kept on all major scientific instruments as well. These notebooks are shared by all the researchers that use the instrument and serve as documentation of the instrument's status and use[6].

Normally a paper laboratory notebook management process includes the following:

- Bound notebooks or loose pages are the two types of laboratory notebooks which are used traditionally. The most commonly used methodology is use of bound notebooks, with a fixed page numbers. Loose pages are used for recording the raw data in the form of printouts directly from the instruments.
- Before issuing it to the researcher a specific number is assigned to each new notebook to keep its traceability.
- The records of the notebook owner and issue date are tracked.
- To keep the authenticity of the entered data in the notebooks, each page of the notebook is signed and witnessed shortly after the records are entered in it.
- In R&D where the data may be of immense importance the witness can be knowledgeable of the data but is not a potential inventor.
- The scientist entering the data in the notebooks should ideally be reviewed by a trained reviewer who should be capable of determining the suitability, accuracy, and effectiveness of the study.
- Archival of the notebooks is an important task achieved by most companies after completion of study[7].

Need of electronic lab notebooks

Although paper retains some advantages in portability and in the ease of entering notes, ELN's have a variety of compelling advantages. The need for manual transcription of data that already exists in electronic form and can directly display the large, multidimensional, and time-dependent data sets produced in modern experiments. Further, they can be used collaboratively by distributed groups and can have automated searching and indexing capabilities to aid in knowledge discovery. ELN's also have advantages in terms of legal defensibility and as records because of the strength of digital signatures and the low cost of storage on digital media respectively[8].

Thus enabling electronic access to lab notebook data might greatly improve knowledge management capabilities, eliminate the waste of information that is inherent in the paper system and improve efficiency by helping to reduce work duplication.

Some other important facts to be considered for the need of laboratory notebooks are:

a. Limitations of paper laboratory notebook
b. Benefits of ELN over paper notebook
c. Preservation of data
d. Ensuring data integrity
e. Tagging information

Electronic laboratory notebook

Electronic Laboratory Notebooks (ELNs) are the state of the art technique for collaborative research in

science. An ELN is equivalent to a paper research notebook. The data which was previously stored on paper, sketches, text, equations, images, graphs, signatures are today recorded on electronic notebook "pages", which can be used in collaboration. The data can be used in the same way as that of a bound notebook. The data entry is usually done with the help of keyboard, sketchpads, mouse, image files, microphone, and directly from scientific instruments. In addition to the basic functions available like a paper notebook, there are a series of functions which make ELN advantageous over the traditional paper notebook. Sharing of data and ability for collaborators in different part of the world can use and share the record of ideas, data and events of the jointly performed experiments and research activities. Also the input of the data (observations/results/instrument data), is easier in ELN[6].

Functionality of ELN[8]

The major components of the ELN are an interactive browser-based client and a web-server-based notebook server. The user is to be provided with a user login and password for maintaining restricted access in the ELN. On login, a table of contents with a user-defined hierarchy of chapters, pages, and notes is displayed on main window. The data entered appears in chronological order and the sub-note can be added if needed, which appears indented and directly after the original note. Thus this technique helps in providing the same methodology of 'writing in margin' of a paper notebook. The discussion or opinions between distributed research members situated all over the world can add data to the ELN which is termed as 'reply'.

ELN is a web- and Java-based application; users may access the pages and notes from their lab or their office at their convenience from Macintosh™, MS Windows™, Linux™, and UNIX™ computers.

With the help of 'entry editors' notes on main page can be added from the main window.

The notebook initially includes editors to create text (plain, HTML, or rich text), equations (LaTeX), and whiteboard sketches, to capture screen images, and to upload arbitrary files. New types of experiments can be recorded with the help of form-based editor by specifying an HTML form that gathers a pre-defined set of parameters and an HTML document that describes how the form data should be displayed on the notebook page (e.g., in an HTML table). On 'submission' the notebook page displays the feeded content and makes it available to authorized members of the ELN. Entries can be repeatedly edited till entries are submitted. The entries submitted appear with the authors name and the date and time of the entry. Individual notes are rendered using external applications (e.g., launching Microsoft Word™), or by using Java applets or plug-ins (e.g., equations, molecular structures, and VRML). Short 'viewer' scripts are also used to check and control how a given type of data is rendered.

Design of ELN[8]

The heart of the ELN comprises of an interactive browser-based user and a notebook server which makes use of a common gateway interface (CGI) scripts that usually run on a web server.

The user interface is rendered by a locally installed Java application that handles user interaction-login, selecting page views, searching, entering notes, signing pages, etc. and the browser, which serves as a launch point and provides displays of individual pages. A small, signed Java applet within the browser launches the application and maintains communication through a socket. This allows the application to request new page views for display in the browser. The applet uses LiveConnect to invoke a JavaScript method to request the page. The server is written in Perl that generates necessary HTML and JavaScript for displaying the initial notebook entry page and for subsequent notebook page views in the browser. It also responds to HTTP requests from the application that implements the basic functionality of logging in, discovering the notebook contents, submitting new entries, etc. The ELN Wizard is a limited client application that encapsulates the entry submission functionality of the client in a form that can be used by other applications without the need for a browser. Because of the clean separation of browser-related code and the modular design of the ELN client, the ELN Wizard is able to re-use many of the client components. The ELN Wizard does not currently handle retrieval or display of notebook entries beyond displaying the notebook table of contents to allow user selection of where new entries should be placed.

The central data management concept in the ELN is the notebook object (NOb), which consists of an opaque, typed piece of data and key/value pairs of metadata-data about the data. The NOb data may be the text, images, or other data composing an entry or it

may be a list of other NObs, allowing representation of the potentially infinite hierarchy of chapters, pages, notes, and sub-notes. The metadata includes a core set of key/value pairs whose meaning is understood by the notebook, as well as arbitrary key/value pairs with meaning for the applications that produce or process NObs. The concept of a NOb, and a core set of keys {authorname, datetime, label, description, objectid, datatype, and dataref} have been defined consistently across many institutional notebook implementations. The dataref key/value allows NObs to reference externally managed data using standard URL notation in cases where the benefits of not making a copy of data within the ELN outweigh the concern over relying on an external system for data availability, e.g., when the data is very large. Representations of the NOb have been developed in Java and Perl, and a flat, MIME-based format is used during exchanges between the client and server and for archiving notebook entries.

At PNNL, we have extended the core metadata set to include standard key/value pairs representing digital signatures, the purpose of a signature (e.g., "authored by", "witnessed by", "approved by"), and the signers' identities. Editors and external applications that create NObs are also free to define new metadata keys. We chose to use Entrust's Java development kit to implement our public-key authentication, encryption and digital signature capabilities, and leverage an installed Entrust public-key infrastructure at PNNL. All signing and signature verification operations occur on the local desktop. As noted, signatures are submitted to the ELN server as NOb metadata. During verification, the signatures and original data are retrieved from the server.

Advantages of ELN

The record keeping in the laboratory has not changed for an era, but today's experiments are changing the face of the record keeping with ELN coming into existence[9]. There is a list of advantages of using electronic lab books over the traditional handwritten versions. The main advantage is knowledge transfer, as with the help of ELN the knowledge can be easily shared with collaborators and colleagues. The information search through the data and information contained within becomes an easier task. The experimental data especially observations and results can be easily integrated. The authenticity of the data makes it a unique one as the data can be one entered and cant be modified. The data recorded will be assigned a permanent date and time record by the software. Thus the electronic records form part of the evidence used in a dispute of patent claims. Good back up and recovery procedures provide a permanent record. The traceability, authenticity and reliability of the data can be assured which is very important. Other minor advantages are note book security, ease of use, interoperability and expandability[1]. ELN supports scientific workflow and also has legal and regulatory support with increased quality in record keeping, better compliance and operational consistency. Thus, ELN provides benefits to scientist, witness manager and benefit for records management.

Industrial application

1. In Pharmaceutical R&D

The pharmaceutical R&D information recorded varies to a wide extent. The scientist dealing in discovery requires a flexible front end that can handle unstructured data and text entry, plus the ability to recognize chemical structures and *in vitro* and *in vivo* study images. From the development and manufacturing scientists perspective a more structured and organized work flow is needed. Thus the multifaceted ELN implementation with separate focuses on discovery and development areas and a shared archiving system will be of great benefit to the direct scientist. After the electronic signatures of author, reviewer, witness the data is locked by converting it to a typical format and then is archived with the help of document management systems.

The ELN plays a very crucial role in pharmaceutical R&D with applications in various departments. The other records maintained with the help of ELN are training records, raw data, inventory, training records, etc.

2. In intellectual property rights (IPR)

ELN can act as a critical domain of IPR. The invention in the form of laboratory findings (observations and results) recorded in ELN make the patent applicant a winner in the patent application race. Initially 'first to file' a patent application was termed as a winner, but today the perspective is changing with the new regulations coming up. The 'first to invent' has the right to obtain patent protection for an invention. Thus lab notebooks (ELN's) form a vital part of any research project. The ELN's, offer secure version control and audit trails to capture the flow of the scientific process, promote collaboration among scientists, and help protect intel-

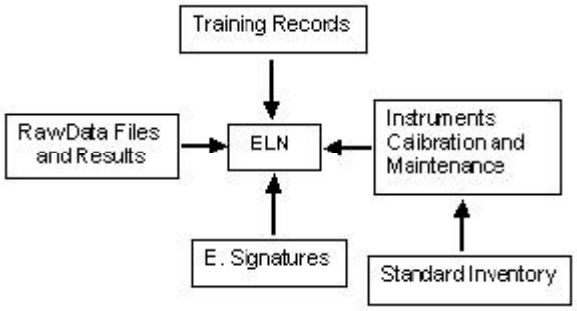

Figure 1: Application of ELN in pharmaceutical industry

lectual property assets. ELN not only protects the IPR assets/invention but also makes the patent applicant a strong holder in today's competitive race of patent application.

Acceptance by regulatory authorities[7]

For a successful implementation of ELN there are a series of requirements to be met. ELN form an important virtue and is very critical document as it becomes a primary record of scientific discovery. This is a crucial part of 'first to invent' for patent claim. With the advancement in software development and 21 CFR (Code of Federal Regulation)[16] coming into existence, regulatory agencies in many jurisdictions accept electronic records. Even the U.S. Patent and Trademark Office has even published a notice stating that electronic records are acceptable in the same way as hand written records but the data generated should be stored in a proper way and should be trust worthy[18]. The electronic records same to paper records are acceptable as evidence of invention in 'first to invent', but the data should be kept properly following Code of Federal Regulation.

But today as such due to fewer cases of existing patent disputes, there is no case law for successful patent defense solely based on electronic storage of data and electronic signature. With the advanced way of record keeping the industry is adopting higher standards than what is defined by law for the storage of scientific data. All the data is governed by the Federal rules of Evidence with two major requirements: business records objection and foundation objections.

US-FDA accepts the electronic records and electronic submissions but has a extensive regulations and guidance[10]. Proper testing and documentation must be available to prove that the system is meeting the user-required functions. With the 21 CFR part 11 compliant software's providing an audit trail the regulations can be met up to a greater extent, ensuring the authenticity of the data generated. The validation of computer systems is a rigorous process of testing and documenting that the computer system meets user and regulatory requirements.

Thus the best interest of discovery scientists should be to maintain properly the validated ELN system for the best responses and acceptance.

Basic regulatory requirements of ELN:

- Restricted access to scientist with different logins.
- To avoid any changes or alteration to be made, the data generated should be locked after the completion of the task.
- Use of 21 CFR part 11 or any other CFR compliance to ensure the authenticity and integrity of the electronic records.
- The timely electronic signatures by author, witness, reviewer and approver ensure the guidelines are followed with good practice.
- With the CFR's involved the audit trails is automatically maintained for the creation, modification, reviewing and approval of records.
- Lastly, the electronic records should always have an accuracy, authenticity, trustworthiness, and relevance.

Limitations of ELN[7]

ELN's have some limitations like other technologies but have to be managed properly. In some case the scientists are not familiar with the data and may make some incorrect conclusions which are a risk of sharing information. To minimize the misinterpretation, and encourage communication between users of ELN data annotation is essential, with clarification of data. The cost involved in comparison to laboratory notebooks is always more as ELN's involve use of computers and software's. Implementing and maintaining integration between ELNs and other computer systems can also be of high cost. Validation of the implemented or upgraded system is a necessary task, to ensure that both user and regulatory requirements are met. Backup and recovery processes must be established to ensure high availability of ELNs and timely recovery of the system in the event of a disaster. ELN's are not portable like bound laboratory notebooks and are fragile. The time involved is more as the data needs to be feeded in ELN's with the help of keyboard which is slightly cumbersome procedure. The other technologies involved are use of

optical character recognition technology, but these technologies are not precise and the scientist does not have much time to check for any software problems while conducting an experiment. The use of software's to draw chemical structures is an accounted problem as it needs expertise to use the tool kit of drawing the chemical structure. Data storage in suitable formats for decades together, generally for a lifetime of a patent, is another challenge with the day to day changing electronic format and archiving media technology.

Market status of ELN

Commercially ELN became available from 1990s, but the market was subdued till 2000. The ELNs available now a day have better technology that concerns with security, legal and regulatory requirements. The number of vendors has increased from very few to 30 recently.

There are no dominant supplier of ELN currently, although some (CambridgeSoft, Symyx, VelQuest, Waters) are considered the first tier for their wider installation base and larger company size.

Pharmaceutical companies that have implemented ELNs include J&J, Merck, GSK, Organon, Berlex, Array Biopharma, Vertex, AstraZeneca, Eli Lilly, BMS and Schering Plough. Many took a hybrid approach to the new technology and used ELNs for data entry followed by printouts[7].

Atrium Research published the results of its 2008 ELN survey. Over 500 scientists, manager, and information technology personnel from 23 countries participated. Interestingly, the vast majority of ELN users express the same data management challenges as non-users. This illustrates how these technologies are just component of a larger information puzzle[11].

CONCLUSION

The ELN has a wide array of applications, starting primarily in the domains of chemistry and biology, to software development. ELN allows researchers, from academics as well as from R&D centers, to access data and notes generated by remote operation of scientific instruments, to maintain Internet accessible personal and laboratory journals, and coordinate work with remote colleagues[8]. The benefits of ELN's clearly outweigh the potential drawbacks and risks associated with the changes in record-keeping procedures. Pilot projects can be undertaken to demonstrate the feasibility of the system followed by full implementation if the pilot project is a success[7].

The adoption of electronic media for laboratory notebooks is not a revolutionary change, but an evolutionary process. ELN acts as the primary research record. The open programming interfaces involved in ELN helps to rapidly customize a notebook to support existing project data types and to integrate the ELN into laboratory processes. The ELN's are not only valuable but also act as robust tools. But some practical issues are still to be resolved to make ELN's a preferred choice across all the R&D's. Nevertheless, it is easy to see that there will come a time when the potential benefits of electronic lab notebooks will outweigh the disadvantages. But the evolutionary process of change will surely be a success in coming years.

If ELNs are compatible with your knowledge management strategy, they are well worth using. Ideally, one should start with a small scale pilot project demonstrating the feasibility of the system. Full implementation can follow if the pilot project is successful.

REFERENCES

[1] J.Landells, H.Palmer; Chemistry in New Zealand, 13 **(2005)**.

[2] K.T.Taylor; Current Opinion in Drug Discovery & Development, **9(3)**, 348 **(2006)**.

[3] Electronic Laboratory Notebook System, Genetic Engineering and Biotechnology News, **25(19)**, **(2005)**.

[4] L.Belenkaia, M.Bohnert, A.W.Liehr; from: http://arxiv.org/pdf/cs.DB/0612123 **(2006)**.

[5] M.Kihlen; DDT, **8(22)**, 1007 **(2003)**.

[6] Geist, J.Schwidder, D.Jung, N.Nachtigal; ORNL Electronic Notebook Project from: www.csm.ornl.gov/~geist/java/applets/enote/

[7] P.Du, J.A.Kofman; JALA, 157 **(2007)**.

[8] J.D.Myers, E.S.Mendoza, B.Hoopes; http://collaboratory.emsl.pnl.gov/resources/publications/papers/ELN.IMSA.final.pdf

[9] D.Butler; Nature, **436**, 20 **(2005)**.

[10] Guidance for Industry Providing Regulatory Submissions in Electronic Format- General Considerations, US FDA.

[11] M.H.Elliott; Electronic Laboratory Notebooks Enter Mainstream Informatics, Scientific Computing, **(2008)**.