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Intelligent Electronic Laboratory Notebooks for Accelerated Organic Process R&D

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Abstract:

Pharmaceutical companies are being forced to find methods to dramatically improve their research and development productivity and efficiency. One approach is replacing the paper laboratory notebooks that have been used in the same way for centuries with an electronic system. An intelligent electronic laboratory notebook (ELN) solution that enables better planning, recording, process optimization, and reporting can enable scientists and engineers to make better decisions throughout organic process research and development, while developing enterprise-wide intellectual capital. The intelligent ELN solution supports the workflow of organic process research and development from route selection through process optimization and validation; process engineering and manufacturing; kilo-lab and pilot-plant operations; and to the creation, review, and approval of product specifications. By implementing best practices learned over the past several years, pharmaceutical companies can now achieve successful intelligent ELN deployments that will provide the gains they so desperately need for their employees and shareholders.

Introduction

The paper laboratory notebook has always served as the central element of organic process R&D activities. Process R&D data must be recorded for archival purposes, and quality experimental information is especially critical during scale-up and technology transfer to manufacturing.[1] Paper laboratory notebooks have been the primary method for capturing and storing data. With the increasing importance of intellectual property to business competitiveness, the paper laboratory notebook has assumed new and increasing significance because it provides the basis for defining priority of invention and is the primary source of information for evidence discovery in intellectual property litigation cases. Additionally, the paper notebook provides proof of compliance with government-mandated procedures.

Beyond their legal, regulatory, and utilitarian functions, paper laboratory notebooks also function as the interface between the individual scientists, their experimental work, and company management. Paper laboratory notebooks provide scientists with a vehicle for expressing, developing, and recording their experimental data as well as their intuition, their concerns or doubt about the rigor of an approach, and the separation between their experimental goals and experimental outcomes. The paper laboratory notebook has therefore been the principal mechanism and embodiment of the company's intellectual capital.

However, the paper laboratory notebook has also become an obsolete tool for managing and sharing information. There has been a strong trend toward the replacement of paper laboratory notebooks with electronic systems, but with varying degrees of success. Through learning developed over the past several years, major pharmaceutical companies are now beginning to globally deploy intelligent electronic laboratory notebooks (ELNs) to their organic process R&D organizations with great success. The time has come to leverage technology to drive efficiency and productivity in organic process R&D.

Strong Drive to Transform Pharmaceutical R&D Process. During the past 10 years, pharmaceutical companies have been under tremendous pressure to transform the business process of research and development, driven by four principal trends:

1. Decline in R&D Productivity. Global R&D expenditures have steadily increased from $27 billion in 1993 to over $48 billion in 2003. During that time, the number of FDA NME approvals changed from 20 in 1993 to 55 in 1996 and back to 20 in 2003.[2] To address this decline in productivity, pharmaceutical companies need dramatically better capabilities to improve the efficiency of their business processes and their scientific staff.

2. Battle for Talent in Western World. The demographics in the United States and Western Europe project a shrinking population of working age people without a commensurate growing pool of young talent, especially in chemistry and other scientific fields. This trend has driven pharmaceutical companies to develop capabilities to capture knowledge produced by their workers and to motivate their existing workers to work smarter.

3. Access to Educated Workforce Shifts to Eastern World. Because emerging nations such as China and India produce science graduates at a much higher rate than Western countries, pharmaceutical companies are locating new research facilities in the Eastern world and outsourcing many noncore activities. To support this trend, pharmaceutical companies need capabilities to connect and integrate their Eastern workforce and partners with their current organizations.

4. SuperNet Organizational Model for Pharmaceutical Companies. Pharmaceutical companies are being restructured as collections of specialist organizations clustered for

(1) Laird, T. *Org. Process Res. Dev.* **2002**, *6*, 1.

(2) U. S. FDA, *Center for Drug Evaluation and Research*, 2004, February, <http://www.fda.gov/cder/>.

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strength and flexibility. To support this restructuring, pharmaceutical companies must develop the capability to disseminate information in a timely fashion, execute closed-loop decision making, and manage an unprecedented degree of collaboration and teamwork.

Unfortunately, the classic paper laboratory notebook and the accompanying business processes are not well aligned with the needed capabilities outlined above. Paper laboratory notebooks consume significant amounts of nonproductive time to plan, record, analyze, report, and communicate experiments and their results. They are ineffective at capturing the full intellectual capital as it is being created, as they are often incomplete due to researcher oversight and lack of standardization. They do not enable information reuse and are an impediment to collaboration, particularly when collaborators are located at different sites or in different countries. They can be lost, destroyed, damaged, or misplaced, making them unavailable for review. Their contents are often difficult to interpret and cannot stand alone because analytical and other supporting information is archived separately. Paper laboratory notebooks cannot support production reports, presentations, and technology transfer operations.[3]

Intelligent Electronic Laboratory Notebooks. To address the deficiencies of the paper laboratory notebook, providers of traditional ELNs have created products in two categories: generic ELNs and specific ELNs. Generic ELNs, also known as nonspecific ELNs, are designed to provide a basic architecture from which users can create a replacement of their paper laboratory notebooks. Providers of generic ELNs include CambridgeSoft, GenSys, Kalabie, LABTrack, NoteBookMaker, and Waters.[4] Specific ELNs are tailored for particular applications and include features of particular use to scientists in the target field. Specific ELN vendors include Cheminnovation, DeltaSoft, Ingenovis, MDL, Rescentris, Synthematix, Tripos, and VelQuest,[4] but the only current provider of an ELN tailored for process chemistry is IntelliChem, Inc..

To provide the capabilities needed to transform the pharmaceutical R&D process outlined in the previous section, IntelliChem developed a set of solutions collectively termed an *intelligent* Electronic Laboratory Notebook (*i*ELN). While traditional ELNs from the companies listed above do little more than replace conventional paper notebooks with electronic versions, intelligent electronic laboratory notebooks encompass domain intelligence (e.g., chemistry knowledge and understanding) that they can apply to the notebook contents. Thereby, they serve as an intelligent assistant to the scientist, which is a chemical development decision-support tool that enables scientists and engineers to make better decisions. The intelligent ELN solution provides the following:

1. Intelligent Planning. The intelligent ELN has the capability to treat materials, equipment, and synthetic procedure elements as first-class objects, which means they can be reused and recombined in new ways without losing elemental information. This allows users to adjust procedures at will (e.g., telescope or scale) because the intelligent ELN automatically recognizes the impact on the associated equipment (e.g., overflow).

2. Intelligent Recording. The intelligent ELN provides the capability to execute protocols and record the accompanying events electronically, including direct data acquisition from equipment/instruments or electronic batch records ("paper on glass").

3. Intelligent Process Characterization and Optimization. The intelligent ELN incorporates design of experiment (DOE) capabilities that allow the user to design an experimental set directed at characterizing and optimizing any given synthetic protocol.

4. Intelligent Analysis and Reporting. The intelligent ELN has the capability to apply organic process R&D domain knowledge (e.g., science and business rules) to stored content and perform intelligent analysis and reporting. Examples include the analysis of notebook content completeness, process flow integrity, process safety, process/equipment compatibility, and process greenness.

5. Intelligent Business Processes. The intelligent ELN has the capability to serve as a framework for executing organic process R&D workflow. For example, Pfizer has used the IntelliChem *i*ELN to manage the workflow associated with the production of active pharmaceutical ingredient (API) for the manufacture of clinical trial materials. Another leading pharmaceutical company has used the IntelliChem *i*ELN to manage the workflow associated with the operation of a high-pressure lab.

Business Context for Use of Intelligent ELN: Potential Benefits. Pharmaceutical organic process R&D has two principal business functions: one, to define a safe and cost-effective route to active pharmaceutical ingredients that ultimately can be used to produce active drug at scale and, two, to produce requisite amounts of active pharmaceutical ingredient (API) that can be used for preclinical and clinical studies. Hence, the business scope of the intelligent ELN is very broad and must serve a wide array of functions.

As an integrated software solution, a complete intelligent ELN would need to support the workflow in organic process R&D in six principal business functions (Figure 1). These business functions and the respective potential benefits from using an intelligent ELN solution are briefly outlined below.

A. Route Selection. During route selection, chemists identify a suitable synthetic route for the preparation of the drug candidate and defining its physical form. The route is often used to produce small quantities of non-GMP drug active for use in preclinical studies. Route selection delivers a sequence of generic recipes, which are scale and equipment independent and are typically summarized in a laboratory process description.

Intelligent ELN Benefits: Usage of the intelligent ELN enables scientists to efficiently search through a document-management database of intelligent ELN records to leverage past experience while avoiding known pitfalls and "recreating

(3) (a) Ramaseshan, S. *Curr. Sci.* **1996**, *70* (11), 950. (b) Pharr, D. Y.; Settle, F. A. *Am. Lab.* **1996**, *28* (14), 35. (c) Lysakowski, R.; Doyle, L. *Records Management Quarterly* **1998**, *April*, 23−29. (d) Dabek, R. A.; Orndorff, J. *ChemTech* **1999**, *29* (3), 6−12. (e) Trigg, J.; Davis, S. *Managing Mod. Lab.* **2001**, *5* (4).

(4) Elliot, M. H. *Scientific Computing & Instrumentation*, **2004**, July.

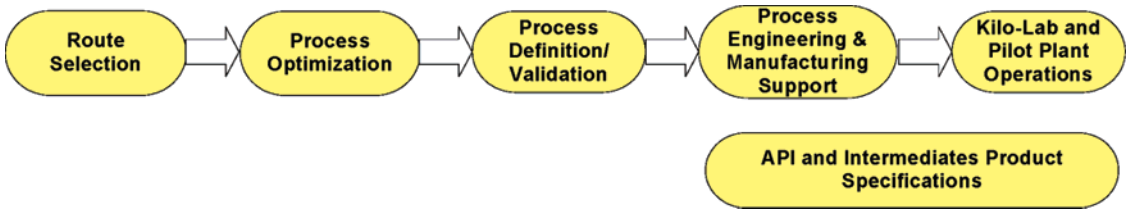

Figure 1. **Organic Process R&D business functions supported by intelligent ELN.**

the wheel." Scientists can use the intelligent ELN to plan, record, analyze, and report on synthetic transformations for a drug candidate. They can then analyze these records to find the suitable synthetic route, which can be stored as a standard method in the document-management database.

B. Process Optimization. Process optimization involves developing the synthetic route into a detailed generic process that has been fully characterized; i.e., critical process parameters have been identified, and the settings for the desired process performance (e.g., yield and quality) have been determined. Process optimization delivers a sequence of generic recipes, which are scale and equipment independent and are typically summarized in a process description. The process description contains descriptions to be used of the analytical methods and specifications for in-process controls, cleaning methods, and safety, health, and environmental (SHE) information.

Intelligent ELN Benefits: The intelligent ELN enables scientists to quickly construct and record detailed procedures, determine the presence of possible safety issues, and save time when sharing the process information with other groups. Scientists can create a generic recipe for each step in the multistep synthesis and then use the intelligent ELN to optimize the process based on product amount or minimized waste. The scientists can use the intelligent ELN to automatically scale the full synthesis for a pilot plant.

C. Process Definition and Validation. During process definition, scientists define the process in terms of scale-up issues. Studies include measurement of process robustness and determination of limits of critical process variables suitable for operation at plant scale. Process definition delivers a sequence of generic recipes, which are adjusted to operating scale and are summarized as a detailed process description. The process description contains mass balance studies and an assortment of safety assessments (SHE-IPC, CIMAH COMAH, NONS).

Intelligent ELN Benefits: Using an intelligent ELN for these activities saves time through the use of DOE and integrated scaling tools that account for characteristics of available equipment. Scientists can create a detailed process description by assembling information stored in the document-management database.

D. Process Engineering and Manufacturing Support. Process engineering and manufacturing support defines the process as it would be operated at scale at a manufacturing site. Tasks include campaign planning and process simulation. Process engineering delivers a sequence of site-specific recipes and their associated equipment requirements in the form of manufacturing instructions for use in the pilot plant and ultimately as a technology transfer document to the manufacturing operations group. Additionally, process engineering provides the necessary documentation for process qualification, process validation, and training materials. Process engineering also provides support for manufacturing operations, especially if technical problems surface later in manufacturing operations.

Intelligent ELN Benefits: The intelligent ELN provides tools to streamline campaign planning, while enabling automatic handoffs to process simulation and other systems. Scientists can create a site recipe at required scale using the specific equipment available at the defined site.

E. Kilo-Lab and Pilot-Plant Operations. Kilo-Lab and Pilot-Plant Operations make and supply active pharmaceutical ingredient for Phase I, II, and III clinical trials under cGMP manufacturing. Kilo-lab and pilot-plant operations use a Site Recipe developed by Process Engineering, associate the appropriate people, equipment IDs, and material lot numbers, and execute the procedure in the kilo-lab or pilot plant under cGMP protocols. Execution consists of one of three scenarios: (1) creation of a paper batch instruction sheet (ticket), which upon completion becomes a paper batch record; (2) creation of a BatchML data file (XML ISA-88 instructions), which can be imported into a manufacturing execution system (MES); and (3) creation of an electronic instruction sheet ("paper on glass"), which upon execution becomes an electronic batch record.

Intelligent ELN Benefits: The intelligent ELN dramatically reduces the time required to generate the required documentation while adhering to regulatory requirements and improving quality by taking into account the appropriate business rules. The intelligent ELN can be used to generate automatic batch records while adhering to FDA 21 CFR Part 11 regulations.

F. API and Intermediates Products Specifications. Specifications for drug substances, final intermediates, drug products, and related materials consist of *tests*, which identify the material in question and characterize its purity and potency, together with *limits*, which are ranges into which test results must fall in order for a sample of the material to meet the Company's internal requirements and/or comply with government regulations. Specifications are required for a material to be used in clinical trials and are also included in filings with government regulatory agencies. They are also used internally as the basis for work guidelines for analytical chemists.

Intelligent ELN Benefits: The intelligent ELN manages the workflow involved with the creation, review, and approval of specifications and provides the most current version of specifications for use in Kilo-Lab and Pilot Plant operations. Additionally, the intelligent ELN supports the

business process for review of batch records and release of product batches by quality assurance.

IntelliChem Approach to Development of Intelligent ELN. Overall, there are significant benefits of leveraging intelligent ELN solutions during each major step of the organic process R&D workflows. Given the broad range of capabilities required for an intelligent ELN coupled with the breadth of the business context for the intelligent ELN, IntelliChem developed a systematic philosophy and approach to the development and construction of an intelligent ELN to serve organic process R&D.

A. Define Intelligent ELN Requirements Using Consortia. IntelliChem's development strategy is to combine our expertise in science, engineering, chem- and bio-informatics, and computer science with an understanding of the needs of our market to expeditiously design, validate, and launch products that fill the needs of that market. To understand the market needs, IntelliChem forms product development consortia and other technical alliances with customers and vendors who serve the market. Consortium members provide IntelliChem with extensive input, validation, and testing of products prior to commercial introduction. For example, IntelliChem Synthesis, the IntelliChem *i*ELN that serves organic process R&D, was developed in a consortium of companies that included Bristol-Myers Squibb, Merck, Pfizer, ChiRex, Sepracor, and Vertex.

IntelliChem's product development consortia are typically nonexclusive arrangements in which we bring together several companies who share the need to solve a common problem. We meet with consortia members on a regular basis during the product development process to review product definition, usability and functional requirements, specifications, and validation and acceptance criteria. Consortium members have estimated that they can obtain more than a one-year competitive advantage in implementing the IntelliChem *i*ELN by participating in such consortia and becoming engaged with the problem being solved.

B. Build Intelligent ELN from a Software Framework. Our experience has indicated that "chemists do not know what they want until they see it." We have observed that requirements and defined needs undergo rapid and continual change during the consortia development processes. These conditions are poorly aligned with traditional software construction processes, which involve a rigid business process consisting of requirements gathering, architecture design, code construction, testing, and validation. Therefore, IntelliChem developed a new agile software development methodology, based on the rapid and iterative creation of prototypes that users could evaluate. Toward that end, we created an extensible software framework of loosely coupled, cooperating objects that could be used to rapidly assemble prototype applications using a minimal amount of "glue code." This software framework, deemed novel by the U.S. patent office,[5] has provided the basis for the construction of all IntelliChem *i*ELN capabilities.

(5) van Eikeren, P.; van Eikeren, J. Object-Oriented Framework for Chemical-Process-Development Decision-Support Applications. U.S. Patent No. 6,-618,852 B1, September 9, 2003, pp 1−63.

C. Capture Intelligent ELN Contents Using Structured Documents. Structured documents are at the core of the IntelliChem *i*ELN solution. Conventional electronic documents, including those produced by traditional electronic laboratory notebooks, are focused on the presentation and format of the contained data. Such documents, often known as "free text" documents, must be interpreted by human experts using domain inference. In contrast, the IntelliChem *i*ELN solution captures content in structured documents, called active experimental documents (AXDs). The focus of AXDs is on data and data semantics (the meaning of the data), in addition to presentation and formatting. Structured documents are composed of data, metadata, and all requisite logical associations between and to internal and external data. These structured documents can be read, interpreted, and understood by computers as well as humans. The result is that structured documents can be transformed, analyzed, and repurposed using computer actions in conjunction with business rules.

D. Manage Intelligent ELN Business Functions via Document-Management Platform. Conventional electronic laboratory notebooks are principally aimed at the planning and recording of laboratory experiments. The IntelliChem *i*ELN solution extends beyond this aim to include management of business functions in organic process R&D. This capability is provided through a document-management platform that provides a collection of services, including the following:

1. Repository services to store intelligent ELN documents in a centralized database;

2. Security management that includes authentication services and authorization services;

3. Workflow and business process management services that include workflow definition, document stages, document routing, notification, and rules-driven actions and permissions;

4. Searching services that enable users to search intelligent ELN records and their content on the basis of a full array of information types, including numbers, text, chemical structures, reactions, retrosynthetic processes, transformations, and related documents;

5. Document-processor services that enable integration of the document-management platform with third-party services;

6. Administrative services to provide metrics and reports on document-management activities including an array of use metrics and audit trails.

E. Provide Intelligent ELN Business Functions via Content Editors. As outlined earlier, the business context of the intelligent ELN for organic process R&D within the pharmaceutical domain is very broad. To support the full range of business functions, the IntelliChem *i*ELN was designed to include a collection of task-oriented content editors that are tailored to each of the various business functions outlined earlier. These content editors employ a common AXD structure, which enables full integration and interoperability between content editors.

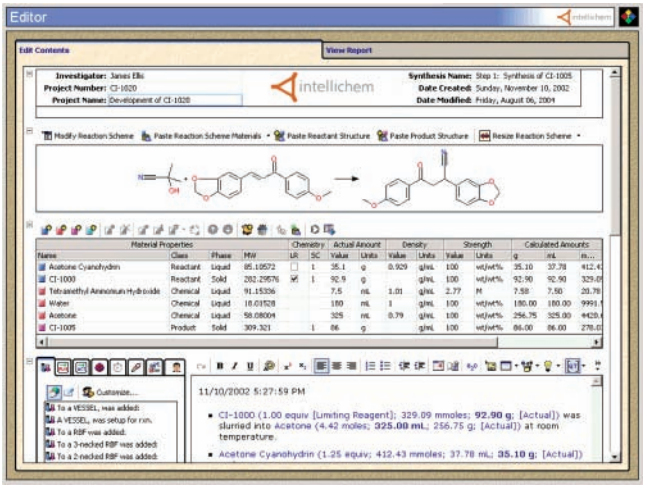

Figure 2. **Content editor for planning and recording chemical procedures.**

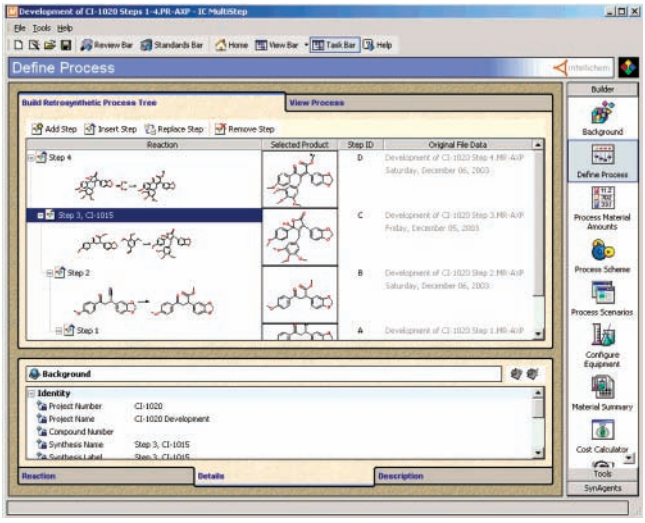

Figure 3. **Content editor for multistep syntheses.**

For example, one content editor provides the capability to plan, record, and report on exploratory chemistry procedures (Figure 2), while others are tailored to support multistep syntheses (Figure 3), library enumeration, and DOE. The IntelliChem *i*ELN includes a generic editor that enables users to assemble their own custom records from existing IntelliChem components and common desktop applications such as MS Word, Excel, and PowerPoint, or an assortment of other desktop applications such as MDL ISIS/Draw. For customers with well-established workflow and business processes that they want to automate, IntelliChem has created custom editors that operate in conjunction with the IntelliChem *i*ELN to automate the required business process. Examples include compound registration, sample management, and paper batch record management.

F. Integrate Intelligent ELN Across Other Drug Development Functions. Within pharmaceutical companies, organic process R&D does not operate in isolation. Rather, organic process R&D works closely with drug discovery, formulated drug product development, analytical R&D, and biological process development. Accordingly, it is critical that organic process R&D can communicate and share information effectively with these parallel functions in drug discovery and development. IntelliChem has created a collection of parallel solutions for each of these areas, making it the only provider of intelligent ELN solutions that span drug discovery and drug development.

Case Study: Intelligent ELN for Organic Process R&D

A principal driver for the adoption of the intelligent ELN from the user's standpoint is that it provides a seamless way to integrate the complex workflow of organic process R&D. The following case study illustrates a pharmaceutical company's implementation of the IntelliChem *i*ELN within their process chemistry division.

The company is one of the world's leading pharmaceutical companies. The successful progression of projects within the company's process research and development division depends on successful management and communication of information between project team members and across projects. However, the information transfer within groups and between groups was impeded by the division's paper laboratory notebook system. With the division's intellectual property being recorded and stored in paper laboratory notebooks, access to the information was limited. The information in the paper laboratory notebooks could not be easily searched or shared. Extensive discussion, explanation, and clarification were necessary to transfer information between groups.

After an extensive evaluation, the company decided in September of 2003 to deploy the IntelliChem *i*ELN globally to 225 process chemists across four process R&D locations in Europe, completely replacing paper laboratory notebooks. Using the IntelliChem *i*ELN, the company's process chemists are able to quickly set up experiment entries and record experimental results and analytical data. The time savings has resulted in a 25% improvement in productivity for the process chemists using the software. Further, because the scientists are able to quickly clone past entries, they have noted a huge leap forward in their reuse of existing information: more than 60% of the experimental entries are cloned from previous work.

The company's process chemists store their intelligent ELN records in the document management database, creating a searchable database of compounds, procedures, results, and other information. The process chemists search the database to locate and reuse information from past experiments. The process chemists have recorded improvements in their ability to transfer information across functional boundaries. Technology transfer has been streamlined, and the process chemists are better able to collaborate across groups, departments, and sites, including sites in different countries.

Discussion

Protection of Intellectual Property Within the Intelligent ELN. Few industries consider intellectual property protection as important as does the pharmaceutical industry. When considering deployment of an ELN, companies must select systems that protect the company's ability to patent and protect inventions. The data contained in laboratory notebooks are used to prove dates of conception of invention

and reduction of the invention to practice. Inventors are instructed to document each step of the inventive process and to have at least one individual witness inventive concepts.

A. Hybrid Systems. While bound paper laboratory notebooks, when properly recorded, signed, and witnessed, fulfill the legal requirements, fully electronic laboratory notebooks have not yet been tested in court. The U.S. Patent and Trademark Office has declared that electronic records are admissible in patent disputes (USPTO Notice 1208 OG 35), but pharmaceutical companies have been reluctant to adopt fully electronic systems. The lack of legal precedent is a commonly cited barrier to widespread adoption of fully electronic laboratory notebook systems.

Consequently, records management departments, who historically have the responsibility for dispensing, tracking, collecting, and archiving the paper notebooks across a corporation, recommend that experimental records from the intelligent ELN be printed and signed as with standard paper notebooks. This has prompted companies to implement a range of "hybrid" solutions, including the following:

1. Sign−Print−Bind. Experiments are recorded, signed, and witnessed electronically. These records are then printed and bound, creating paper documents of record.

2. Print−Sign−Bind. Electronic records are printed first and then signed and witnessed via the conventional signing process. The signed records are then bound, and the bound notebook is handled by existing procedures.

3. Print−Sign−Binder. Electronic entries are printed on prenumbered punched paper. The records are signed and witnessed, and the paper documents are inserted into a three-ring binder. PatentPad (Scrip-Safe, Loveland, Ohio) manufactures special paper for this purpose, which is unique and cannot be photocopied.

4. Print−Sign−Paste. Electronic entries are printed and pasted into paper laboratory notebooks. The records are then signed and witnessed via the conventional process. This is the least desirable option but represents the most common initial implementation because it employs existing business processes.

B. Completely Electronic Systems. The ability of an intelligent ELN to capture accurate information during the invention process may actually exceed that of paper. Examination often reveals that paper records are not signed contemporaneously but are signed and witnessed long after the work is done, typically in batches. This makes the "read and understood" aspect of record witnessing questionable given that many pages are signed at once. By contrast, the signing and witnessing of records in the intelligent ELN can be automated, tracked, and enforced by the workflow capabilities of the intelligent ELN. For example, in a typical intelligent ELN implementation, the signing and witnessing workflow is carried out as follows:

1. The user creates a new intelligent ELN record, checks it into the database, and applies an "in-progress" status to the record. The electronic signing process is tracked by the system, establishing the priority date for the contents of the record.

2. Later, the user checks out the record to add information. The user then deems the experimental record completed and checks in the document, promoting the document status to "completed and ready for witnessing."

3. Promotion to the new status triggers the following sequence of events: (a) the permissions for the document are adjusted so that the document cannot be modified further; (b) a preselected witness is notified by e-mail and reminded that he/she has a document to witness; and (c) the witness reviews the document and promotes the status to "publish."

4. Promotion to the "publish" status locks the document to further changes but makes it accessible in a read-only state to users, who can then find it in searches and use it as a starting point for new experiments.

Today, there is pent up demand to go completely electronic within the scientific and information technology (IT) communities.[6] By the end of 2004, at least two of the top 10 pharmaceutical companies will have converted to completely electronic intelligent ELN systems within their process R&D divisions.

Global Deployment of IntelliChem i*ELN*. A. Hurdles to Adoption: Data Standards and Integration. From the end-user standpoint, the critical success factors in the deployment of an intelligent ELN are global access to data, interoperability with their tools, and integration with their workflow. Failure to properly address these success factors results in end-user push back, ultimately resulting in a failed adoption. In any deployment, IntelliChem's focus is on delivering integrated data, as this gets end users involved.

Achievement of these critical success factors within the pharmaceutical industry is challenging because, historically, pharmaceutical companies have viewed their unique technologies and business processes as competitive advantages. Hence, many companies report that they are using "proprietary" internally developed data standards. To compound the problem, this proprietary mindset has prevented bio-pharmas from openly collaborating to establish industry standards. By sharp contrast, other research-intensive industries, such as telecommunications, have established consortia that have set standards that benefit the whole industry. The trend is now reversing in the pharmaceutical business. IntelliChem has successfully formed consortia consisting of vendors and pharmaceutical companies who are competitors. These consortia have defined standards upon which solutions to common industry problems can be built.

Integration of data flow represents one of the biggest hurdles to successful adoption and realization of the benefits of an electronic laboratory notebook.[7] For many years, the pharmaceutical industry has been building proprietary informatics systems as well as adapting a variety of commercially available systems for data collection, data management, project management, and other data-related business and scientific functions. Historically, because of their proprietary nature, the flow of data from system to system has been inhibited. For the end user, this results in duplicate data entry, inefficiency, and poor decision-making due to

(6) Coles, S. *R&D (Cahners)* **2002**, August.
(7) Coles, S. *Pharmaceutical Visions* **2002**, Spring.

not having the right information at the right time. Accordingly, customers evaluating electronic laboratory notebooks look for integration capability and adaptability.

B. Hurdles to Adoption: Corporate Culture. The highest hurdles to adoption, though rarely discussed, are embedded in the pharmaceutical industry's own culture.[8] These hurdles fall into three broad areas: (1) corporate aversion to risk; (2) personal aversion to risk; and (3) fragmented and heterogeneous organizational structures.

Corporate Aversion to Risk. Drug discovery and development is an intrinsically risky business. Pharmaceutical companies spend on average more than $1 billion over a 12- to 15-year period to bring a new drug product to market. Hence, organic process R&D personnel are driven to create explicit and tightly managed operating practices. Additionally, the industry operates in a highly regulated environment where the penalty for failing to comply with FDA requirements can be catastrophic. Companies rely heavily on standard operating procedures (SOPs), current good manufacturing practices (cGMP), good laboratory practices (GLPs), and well-defined development planning, implementation, and corporate reporting mechanisms. This environment produces a distinct side effect, namely a high corporate aversion to risk. This hinders pharmaceutical organizations from broadly adopting innovations such as electronic lab notebooks because they fear changing long-established SOPs and derailing development projects already on a tight timeline. Ultimately, this cultural condition prolongs the pilot-testing phase, entices companies to contain adoption in order to carefully study the impact, and delays the receipt of return on investment (ROI) and collateral benefits.

Personal Aversions to Risk. Development scientists typically are concerned about endorsing novel approaches for fear that they may not work out and that the failure may damage their reputations. In addition, development scientists carry the burden of rigid regulatory, operating, and budgetary controls, along with high demands on their schedules and performance. Most process R&D staff members have little time to investigate technology vendors, and they typically lack management's support to embrace and promote serious technology innovation. Technology pioneers within organic process R&D are rare. When they do exist, they are most often found at the more senior levels, levels where it is difficult to translate the vision into corporate practice. This results in a predisposition to prolong the pilot-testing phase, which again delays the receipt of ROI and collateral benefits.

Fragmented Organizations. Large pharmaceutical companies are culturally diverse and geographically dispersed. This is not an optimal environment for fostering collaboration and innovation. Project teams within functions, even those working within the same site, rarely compare notes and share information. Initiatives embraced by one site often fail to carry across other sites,[9] and innovations are not deployed across the corporation. This fragmented organizational environment makes it challenging to target companies effectively. Vendors have limited resources yet must call on multiple individuals within the same pharmaceutical company, thereby extending already costly sales cycles. These conditions not only drive consolidation and divesture in the vendor market but also contribute to pharmaceutical company perceptions that electronic laboratory notebook products may be immature, unstable, and risky.

C. Successful Adoption: What Have We Learned? Over the past six years, IntelliChem has recognized the hurdles above and has found methods to address them. As a result, we are working with a number of companies that have embraced the IntelliChem *i*ELN wholeheartedly. What accounts for this difference? We have had the opportunity to study and learn from 7 of the 10 largest pharmaceutical companies as they have endeavored to transition from paper notebooks to an intelligent ELN. Companies have taken varied paths, but they have shared four common strategies:

1. Committing the Company. Companies implementing an intelligent ELN have an organizational commitment to the project. While some companies commit via senior-management edict, others have used a grassroots approach, often championed by a single, determined individual. The common element is a commitment not just for a pilot program but for a long-term commitment to solving a business problem.

Competent leadership supported by a mandate from top management is of the utmost importance. Strong leadership, broad authority, and attention to "change management" are critical factors. Early engagement and alignment among end users and management at all sites is crucial. Additionally, all business functions and procedures that are affected by the intelligent ELN must be reviewed and adjusted as necessary. An intelligent ELN implementation is not a project driven by technical IT leadership. The implementation needs to be overseen and supported by someone who recognizes the company's business objectives.

Long-term commitment to the project is key because an intelligent ELN is a disruptive technology. Its implementation can threaten the position and responsibilities of some employees. Stepwise implementation with clear and open goals reduces the threat. Additionally, clear signals from senior management provide necessary motivation for success. Companies with successful intelligent ELN implementations have recognized the value of this technology and have developed detailed, realistic, and long-range plans for implementation.

2. Investing in Resources. After adequate commitment, successful companies recognize that an intelligent ELN implementation requires an investment in resources and time, sometimes more than originally planned. Team members may need to be relieved of some normal responsibilities to focus on deployment requirements. Training must be provided to the new end users and must be ongoing. People are the most important resource of any organization, and they are also the most valuable resource for intelligent ELN implementations.

Additionally, the project may require expenditures for the support of the technology infrastructure. For example, laboratories may require the addition of new or upgraded computer hardware and the appropriate network connections and bandwidth.

(8) Bruce, S. *Laboratory News* **2002**, April.
(9) Rooney, T. A. *Today's Chemist at Work* **1999**, August 15.

3. Developing Best Practices. Major and lasting benefits of an intelligent ELN implementation depend on the development of and adherence to best practices. Firms with successful intelligent ELN implementations have chosen a variety of approaches, from Continuous Improvement to Six Sigma to classic business-process re-engineering, but all have involved detailed process mapping, system analysis, baseline benchmarks, clear and relevant metrics, and a commitment to root-cause analysis and diagnosis. By understanding the capabilities of the intelligent ELN software, creative project teams are able to reengineer the laboratory record management process to better utilize the benefits of the intelligent ELN.

4. Moving Beyond Pilots. Pilot projects for electronic laboratory notebooks have been around for many years.[3d] In most pilot projects, the aim has been typically fourfold: (1) determine if the technology is mature enough to be useful; (2) determine if the value is as advertised; (3) determine if people accept it; and (4) determine if it will scale. Unfortunately, many pilot projects have failed to lead to full-scale implementations. Early problems with electronic laboratory notebooks involved vendor inexperience, lack of global support and global connectivity, and misjudgment of required resources. Some companies conducted pilots with no plan for full deployment if the pilot was successful.

In our experience, the successful deployment of enterprise intelligent ELN requires a significant amount of confidence and patience. Through short-term pilot experiences and common sense, successful companies recognize the benefits of the intelligent ELN in terms of higher-quality data, more visibility of project activities, and cost/time saving. They also recognize that these savings can develop only with experience, process re-engineering, and attention to change management. These companies have set metrics and ROI measurements that extend over reasonable time periods and involve both tangible and intangible benefits.

Future Direction for Intelligent ELN. Electronic systems such as the intelligent ELN continue to develop and mature rapidly. The four main thrusts of direction for the intelligent ELN in the future are (1) increasing levels of intelligence, (2) increasing levels of integration, (3) continued strides in ease of data entry, and (4) improved management reporting and data mining.

A. Increasing Levels of Intelligence. Today's intelligent ELN solution is intelligent in many ways, ranging from intelligent experiment planning to intelligent reporting analysis to intelligent business process management. Soon, these systems will also have the ability to do additional types of intelligent "scoring," such as for safety and greenness. In the United Kingdom, safety assessment must be completed before execution of all experiments involving hazardous substances. Such assessments are both time-consuming and challenging to less experienced chemists, making compliance difficult. Future intelligent ELN solutions will enable chemists to quickly rank all their planned experiments by a "greenness score," essentially making greenness part of the decision-making process rather than an afterthought.

B. Increasing Levels of Integration. Data standards are already driving integration between the intelligent ELN and other systems, and integration improvements are bound to occur. First, equipment manufacturers will adopt data standards as outputs for their hardware. As this occurs, the intelligent ELN will become the central repository of all data within organic process R&D, eliminating the need for systems that exist merely to store such data. Second, integration with free-text data sources (e.g., CrossFire for Beilstein and CAS SciFinder) will become commonplace. Third, and perhaps most importantly, pharmaceutical and biotechnology companies will approach the intelligent ELN as an enterprise-wide business capability that spans drug discovery and development. This will lead to broader deployments that include scientists and engineers from discovery chemistry and biology, process R&D, formulations, analytical, and bioprocess organizations.

C. Data Entry. As with all enterprise software categories, intelligent ELN users will continue to evolve in terms of their interaction with the system. As their usage evolves, so will their desired input methods. At the same time, technology is rapidly improving in the areas of speech recognition, handwriting recognition, and wireless connectivity for mobile devices. Some users already use barcode scanners in laboratory settings to input data, and this trend is sure to continue. The use of the Microsoft Windows XP Tablet PC is also gaining in popularity. In the future, intelligent ELN users may be able to access the system and enter data through just the power of their voices.

D. Management Reporting and Data Mining. The first major step toward managing R&D organizations electronically is creating electronic data. The intelligent ELN solution is a lynchpin in the creation of such data. Once adoption is broad among the scientists, all kinds of analysis and data mining will become possible. Analysis interfaces will allow management to aggregate campaign costs, analyze trends at the bench and project team levels, and gain insight into laboratory spending. These analyses will quickly lead to better and faster decision making at a corporate level, ultimately improving the output of R&D organizations.

Conclusions

The pharmaceutical industry now faces a tumultuous period. Drug companies are grappling with depressed rates of innovation, anemic pipelines of drug candidates, and a dramatic drop in funding from blockbuster candidates. The pharmaceutical industry is primed for a new generation of solutions that can serve as the basis for dramatic productivity improvements in organic process R&D. These solutions are built on a foundation of open architecture and industry standards, and the technology offers sufficient flexibility to meet the growing needs of the industry.

Paper laboratory notebooks are no longer a sufficient solution to knowledge management and intellectual property protection of organic process R&D activities. An intelligent ELN solution enabling higher quality data storage, use, analysis, and management enables pharmaceutical companies to excel in the current environment. This tumultuous period demands that the pharmaceutical industry evaluates how an intelligent ELN solution can be more effectively and more rapidly adopted. Intelligent electronic lab notebook adoption

is brisk among a subset of pharmaceutical companies. Those companies engaged in intelligent ELN deployments are integrating the technology with their own enterprise solutions.

Implementation of the intelligent ELN is a radical change to the business process of organic process R&D. It has the potential for huge payoffs in quality, time, and, if done right, money. However, there are a great number of hurdles and possible diversions, and these must be addressed in order for an implementation to be successful. When successful, the deployment of an intelligent ELN solution will enable the company to better archive, manage, analyze, and protect its intellectual property. The company will achieve a significant acceleration in organic process R&D, there will be fewer surprises in API production, and the company will have a strategic advantage over its competitors.

The question then becomes, "If not now, when?"

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