Takeda Pharmaceutical's E-Notebook Project Report

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Takeda Pharmaceutical Company Limited faces three problems: controlling cost and time in activities to discover drugs, finding a solution to patent disputes, and helping Fujitsu's customers to observe compliance. To solve these problems, Takeda Pharmaceutical Company Limited and Fujitsu Limited cooperated to establish E-Notebook and its related effective systems, which are a long-term signature system, a system to check regulatory controls on chemical compounds and a chemical compound database system. These can be used to thoroughly computerize information on drug discovery. As a result, we have improved systems to input and record data in compound synthesis studies, helped organizations observe compliance by protecting against synthesis of illegal chemical compounds and made it possible to establish evidence on the date of a drug's discovery with an electronic certificate. We have improved the quality of customers' drug discovery activities by realizing measures to resolve patent disputes, helping them observe compliance and improving the operations of customers' researchers.

1. Introduction

Fujitsu has worked to improve the efficiency of drug discovery research including chemical compound synthesis and to accumulate and promote the use of in-house knowledge of pharmaceutical companies. As part of its activities for this purpose, Fujitsu has rolled out a solution business using ChemBioOffice Enterprise Suite, a chemical research information management system including an electronic laboratory notebook feature (E-Notebook) provided by PerkinElmer of the U.S., and striven to improve the research work of pharmaceutical companies for almost 15 years. Recently, pharmaceutical companies have been faced with the following issues in developing new drugs.

- Control of cost increases
- Improvement of efficiency of patent operations and measures to deal with disputes
- Regulatory compliance[1),2)]

In order to resolve these issues, pharmaceutical companies are working to improve operations by reducing development and patent application periods while lowering development costs and achieving regulatory compliance at the same time. As a solution, information and communications technology (ICT) has been introduced into drug discovery research operations mainly at overseas pharmaceutical companies. A major Swiss pharmaceutical company, F. Hoffmann-La Roche, built a knowledge database called ROCK in its drug discovery research laboratories and presented the results in a paper in 2011.[3)] The building of ROCK was started in 2005 and the system, which stores 900 entries as of 2011, is used by a few hundred drug discovery chemists every month. Linking with other databases is also planned.

In Japan as well, major pharmaceutical companies have been rapidly moving ahead with the introduction of ICT into drug discovery research operations in recent years. While it was mostly introduction of applications capable of drawing chemical structural formulae in the 1990s, in the 2000s, introduction of electronic lab notebooks (e-notebooks) containing records of compound synthesis research (chemical equations) started on a large scale. In the 2010s, in view of moves to improve the efficiency of research operations on a company-wide scale as well as management of research records at the individual level, an ideal form of e-notebook

system has been studied. It should be capable of linking with other systems and have features that improve the efficiency of many research-related operations in addition to management of research records.

Fujitsu constructed an E-Notebook system jointly with Takeda Pharmaceutical Company Limited (Takeda Pharmaceutical) in 2009 and solved the following key issues with every major system update over three years since the start of operation in Mach 2010.

- Centralized storage and management of laboratory data to prevent risks such as loss and alteration
- Standardization of lab notebook descriptions to maintain the quality of descriptive content
- Reduction of time required for notebook writing, creation of various reports and preparation of patent specifications
- Accumulation of reaction information for sharing of synthesists' knowledge
- Regulatory control system linking to facilitate compliance and avoid risks

This paper describes the E-Notebook project that has been promoted to solve these issues by presenting the background to its introduction, an overview of E-Notebook and peripheral systems and its effect of helping to solve the issues.

2. Background to introduction of E-Notebook

In research on chemical compound synthesis, types of reagents and conditions of synthesis are recorded in lab notebooks for use as supporting materials in creating patent specifications and research papers. Starting in the 1990s, applications for drawing chemical structural formula including ChemDraw of PerkinElmer (then CambridgeSoft) were developed, and they made it easy to accurately draw chemical structural formulae and marked the first step toward applying ICT to lab notebook creation. However, the final form of management was printed material (paper), and this medium is still used by many companies. An increasing number of companies have recently been reconsidering this and computerizing lab notebooks, the reasons for which include the following issues (**Figure 1**).

1) Reduction of costs/periods of research operations

With new drug discovery becoming increasingly difficult year by year, research and development periods and costs are in an increasing trend. Recently, as a result of development competition between pharmaceutical companies, existing therapeutic drugs have come to show sufficient effects and generic therapeutic drugs are required to offer higher efficacy and safety than the existing ones. This has led to an increased scale of clinical tests, in which drugs are administered to people for confirming efficacy and safety. Consequently, costs of 30 billion to 100 billion yen are now required for developing one drug and reduction of the costs and periods of development poses an issue.

One effective way to overcome this issue is to have supplementary information by promptly sharing synthesis research information between in-house researchers, but such sharing with paper media obviously takes a tremendous amount of time and trouble. Even if information is shared, any description or expression peculiar to a particular researcher may hinder effective use of the information provided.

2) Improvement of efficiency of patent application-related operations and protection from disputes

For pharmaceutical companies, patents are important management resources and closely related to a problem called the "patent cliff," in which sales and profits significantly decrease. A patent cliff is a phenomenon that arises after the patent of a new drug expires, and inexpensive generic drugs with the same active ingredients appear on the market causing the sales and profits produced before the expiration of the patent to abruptly drop, and having a serious impact on corporate management. For that reason, prompt patent application and protection from disputes are an important issue for any research department.

Lab notebooks have the role of storing materials that can be used to identify the time of development

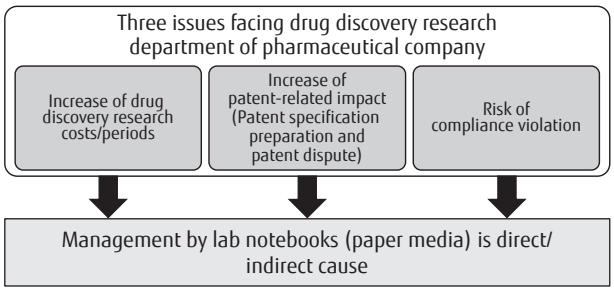

Figure 1
Issues facing pharmaceutical companies and their causes.

and used when preparing specifications for a patent application. Accordingly, it is essential that evidence in an unalterable form for identification of the date and time (seal of approval) should be recorded in lab notebooks.

However, creating lab notebooks (sheets) by handwriting or printing potentially has risks in patent application such as "clerical errors in and alteration of the content of lab notebooks," "loss of lab notebooks due to accidents and disasters" and "low evidential competence for identification of the date and time." It is necessary to reduce these risks by making use of ICT.

3) Prevention of synthesis of illegal chemical compounds

Possession or synthesis of some compounds is restricted by regulatory controls of Japan and/or foreign countries. Synthesizing compounds that are subject to regulatory controls seriously affects corporate compliance and must be strictly avoided. While there are check systems to see if a certain compound is subject to regulatory controls, transcription errors or failure to conduct regulatory control checks by researchers cannot be completely prevented if lab notebooks are in paper media.

For Takeda Pharmaceutical, which had these issues to deal with, Fujitsu proposed in 2009 a migration to a completely electronic solution capable of recording and managing synthesis research records related to compound synthesis without the need for paper media and linking of E-Notebook, a package of ChemBioOffice Enterprise Suite provided by PerkinElmer, with its related systems (**Figure 2**). E-Notebook is a package product intended mainly for pharmaceutical companies that realizes input, search and display of information on compound synthesis experiments.

To address the issue of identifying the date and time of development, which cannot be solved with E-Notebook alone, we linked the system with a long-term signature system that makes use of a timestamp service in order to improve efficiency of both research and patent application operations.

3. Overview of E-Notebook and related systems

1) E-Notebook

E-Notebook is a package that is at the core of the complete electronic solution that has been introduced. It is equipped with a screen structure and functions optimized for synthesis research records. One of its characteristic functions that differentiate it from ordinary business management systems is that implementation of ChemDraw for drawing chemical structural formulae makes it possible to efficiently draw chemical structural formulae, which are cumbersome to input.

There are many other functions for improving the

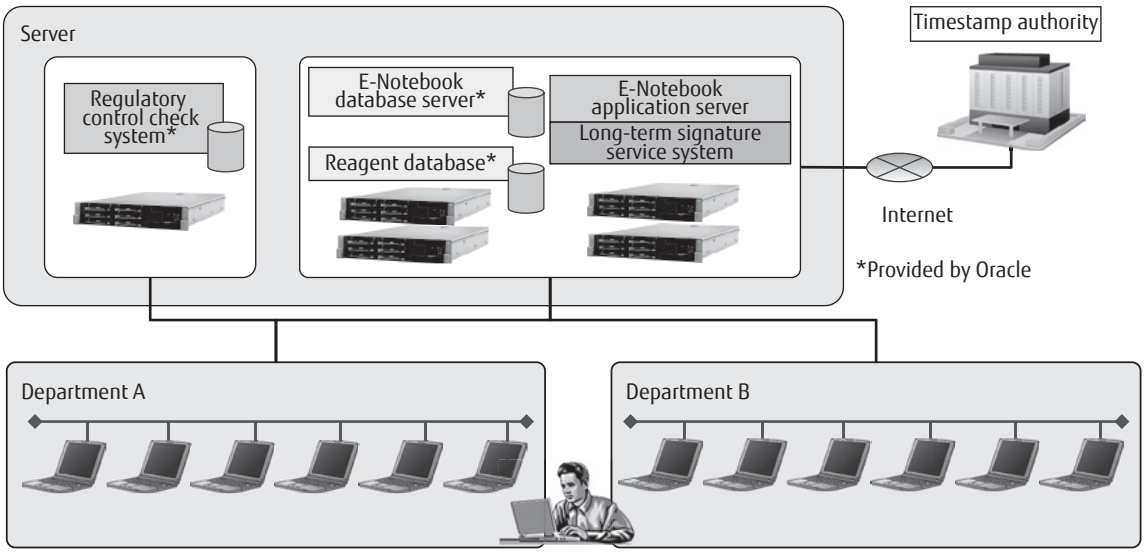

Figure 2
Image of E-Notebook system for Takeda Pharmaceutical.

efficiency of compound synthesis operations. It can automatically calculate molecular weight and molar equivalent based on the amount of reagent and molecular weight. This allows researchers to obtain values required for experiment records, which were previously obtained by manual calculation, simply by inputting chemical equations and the weights of the reagents used for experiments.

E-Notebook is equipped with a synthetic pathway diagram display function (Batch Explorer). This function can associate between lab notebooks when research records are input and the compounds in the synthetic pathways associated can be ultimately listed for display. In most cases of synthesis research, a synthesized compound is used as a material for subsequent synthesis, or an intermediate, and this process is repeated several times until the ultimately intended compound can be obtained. When sorting out synthetic pathways up to the obtainment of the final compound for reviewing experiment records or applying for patents, the synthesis pathways should preferably be displayed as a list. To meet this demand, a function of indicating synthetic pathways in the form of a tree diagram (offered by Batch Explorer) can be used for visual confirmation of the system of synthesis.

On top of this, a function called AutoText can be added that provides fields for inputting records required for compound synthesis research, the layout of which can be changed according to the operation, and it supports input of set phrases. With this feature, different research operations of various departments can be flexibly accommodated by making configuration changes.

2) Linking with reagent database

E-Notebook has a function of linking with a reagent database that is provided to help researchers input chemical structural formulae. Some compounds used as reagents of compound synthesis contain more than 100 atoms, and they not only require a large amount of time for drawing but also may cause a serious impact on subsequent patent applications depending on the type of clerical errors that exist, if any. To deal with this problem, E-Notebook can be linked with a reagent database containing records of chemical structural formulae of reagents. This allows accurate chemical structural formulae to be obtained and directly reflected in the chemical equation drawing fields of lab notebooks simply by providing reagent catalog numbers and CAS numbers, which are information allowing reagents to be uniquely defined. In this way, a significant reduction in the time required for input and prevention of clerical errors have been realized.

3) Regulatory control check system

The regulatory control check system is linked with CRAIS Checker, a system to check for controlled substances provided by Patcore Inc., and it has been adopted by Takeda Pharmaceutical. To ensure that a regulatory control check on compounds is always performed when researchers input research records, the system is built to carry out a regulatory control check on input chemical equations when lab notebooks are approved (Sign & Close). This feature allows researchers to spot any controlled compound recorded in a lab notebook without any trouble. For improved detectability, the system adopts color-coded screen indications of red and yellow in the screen according to the degree of importance of regulatory controls.

4) Long-term signature service system

The long-term signature service system, which is composed of digital signatures and timestamps, is a technology that provides electronic records with evidential competence equivalent to that of a signature and seal affixation over a long term and provides important ICT in complete computerization of lab notebooks.[4] This service allows lab notebooks to be recorded in electronic media and the date and time of implementation of what is in the description can be easily verified independently.

For this service, we have adopted PFU Timestamp Service (integrated into SEIKO Timestamp Service of Seiko Solutions Inc. in June 2013) and implemented it as a feature that provides electronic records with long-term signatures combined with timestamps in conjunction with Sign & Close of research managers.

4. Effect on solution of issues

The introduction of E-Notebook has brought a tangible improvement to the efficiency of research operations, efficiency of patent operations together with measures to deal with disputes, and regulatory compliance in research operations, which have been longstanding issues (**Figure 3**).

1) Effect on synthesis research

Automatic stoicheiometric calculation, which is a standard function of E-Notebook, and the AutoText

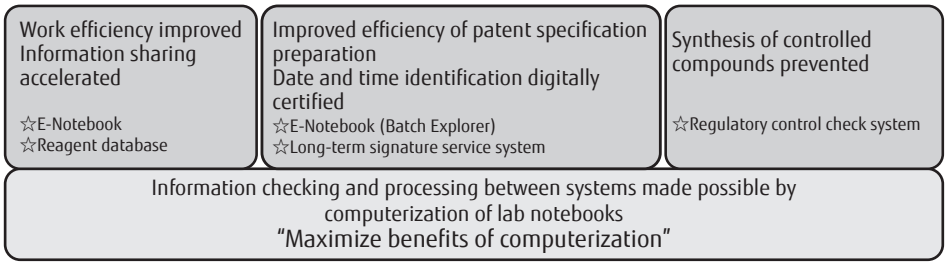

Figure 3
Effect of introduction of E-Notebook.

function for input standardization can be used to support input because it is possible to show most of the information required for research records simply by inputting experiment information. In addition, combining the automated input of compounds containing many atoms by using a reagent database reduces the time required for researchers to input research information to half or less from recording in lab notebooks.

Improving input efficiency by these means leads to standardization of recording formats, and this has proven to be effective in aiding information sharing between researchers. For example, its application to cross-referencing is becoming widespread because it helps researchers in the lab acquire information related to the compounds required. In addition, its application to cross referencing is becoming widespread.

2) Effect on patent application operations

Batch Explorer can be used to gain an overall view of all the synthesis pathways, which has dramatically improved the efficiency of processes up to preparation of patent specifications as compared with recording them in paper media or files in Word or another format. In addition, use of the long-term signature service system automatically gives digital signatures and time-stamps to lab notebooks that have undergone Sign & Close, and this allows computerization of approval and date and time identification. This offers measures to deal with patent disputes related to development date and time without increasing the operational burden.

3) Effect on regulatory compliance in research operations

Researchers can now efficiently check regulatory controls on chemical compounds to be synthesized in the experiment planning phase by linking with CRAIS Checker. This has improved operations and demonstrated its contribution to compliance activities of a research department because there have been no cases found of unintended synthesis or registration of any controlled compound since the start of operation in March 2010.

5. Conclusion

Along with the increase in number of lab notebooks registered, the focus of future issues is shifting to improving processing performance, which includes speeding up screen transitions and search, and demand for stable continuous operation of the system. This proves that E-Notebook has become an important platform system essential to a drug discovery research department and there is huge demand for an improvement of its quality. To address these issues, we have collaborated with PerkinElmer and relevant software and hardware support companies to work on steadily improving the operation and maintenance activities.

We completed the fourth update project in January 2014. One target of this project is to begin earnestly making research information into a knowledge database. This approach will be the first step toward innovating drug discovery operations, which is what Takeda Pharmaceutical and Fujitsu aim at, and its result is expected to have an influence on the ideal form of future drug discovery research.

Fujitsu also has ICT drug discovery solutions that make use of supercomputers. We intend to continue making contributions together with customers to new drugs useful for the health of human beings while pursuing the ideal of next-generation drug discovery, integrating the knowledge of front-line drug discovery researchers and utilization of supercomputers.

Messrs. Tsutomu Morita and Seiji Fukui of Takeda Pharmaceutical Company Limited, who are in charge of this project, and other relevant people have offered

great support for utilization and stable operation of the system. We would like to take this opportunity to extend our deepest appreciation to them.

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