Organic Process Research & Development **2004**, *8,* 983–997

Articles

Sanofi-Synthelabo Chemical Development and the Development of an Electronic Laboratory Notebook

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Abstract:

Past attempts to develop electronic laboratory notebooks (ELN) have not always met with the success expected of them. This may have been due to job aspects and the difficulties encountered in their practical application, insufficient support provided to users during the learning phase, application complexity, interfacing problems with preexisting information systems, and the necessary integration of regulatory and legal aspects. Sanofi-Synthelabo adopted a different approach by emphasizing practical application and user support while putting the regulatory aspects to one side. An ELN model was developed on the basis of initial user-derived specifications, and a prototype was then produced, known as Kalabie (Klee business software). This ELN is sufficiently flexible to be shaped for different specialized chemical development sectors (synthesis, automates, preparative chromatography) and interfaces with preexisting in-house Oracle and MDL databases, thus supporting multisite extensions as a user-friendly intranet application. Technicians, scientists, and managers were happy with Kalabie when it entered service. Work is ongoing to extend the use of the ELN and to integrate the regulatory aspects.

1. Introduction

The electronic laboratory notebook has long been a dream of organic chemists. Although the will to develop such a tool was great, its actual production was for many years hindered by immature technology, particularly as regards systems operating on a company-wide scale. However, as technology advanced, the dream of the electronic laboratory notebook appeared to be approaching reality. Thus, at the end of 1998, Sanofi-Synthelabo's industrial chemical development (ICD) unit decided to address the issue and thereby facilitate the daily tasks of its chemists and free them from paper notebooks.

A certain number of other pharmaceutical companies also entered the running. When the project started, few electronic

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10.1021/op040012v CCC: $27.50
Published on Web 10/05/2004

Table 1.

company	electronic laboratory notebook	site address
Cambridge	Soft E-Notebook	www.cambridgesoft.com
Mdl	Elan	www.mdl.com
Intellichem	IDS	www.intellichem.com
ACD	chemfolder	www.acdlabs.com
Avatar	Labtrack consulting	www.labtrack.com
ChemExper	Expereact	www.expereact.com
Tripos	Tripos Electronic Notebook	www.tripos.com
Creon Lab Control	Dragon	www.creonlabcontrol.com

laboratory notebooks were available on the market. Since then, several applications have seen the light of day. Given that the aim of this paper is to describe the product developed by Sanofi-Synthelabo, we shall not focus on a description of these different electronic laboratory notebooks, but shall cite simply for information their main representatives (see Table 1).

Although the idea of developing an electronic laboratory notebook was certainly tempting, we knew that projects of this type had not always met with success in pharmaceutical companies. Aside from the technical difficulties, the main obstacles were identified as follows:

(i) end users could be reluctant, notably if the application did not correspond perfectly to their process,

(ii) the return on investment in such a project was very difficult to evaluate,

(iii) issues concerning regulatory compliance and intellectual property rights (legal value of electronic recordings) were unresolved,

(iv) an electronic laboratory notebook is a system, i.e. not only an IT application but also a set of procedures supported by a suitable organisation, which makes it a complex project,

Obviously, these risks were offset by the various advantages we would gain by taking the project to a successful conclusion:

(1) Full use of the company's chemical heritage by facilitating the search for and sharing of corporate information. An electronic laboratory notebook of course accelerates text-based searches (by author, by key-word, etc.), but also more complex searches impossible to perform with paper notebooks (searches based on structure, sub-structures, multiple criteria, ...).

(2) Improvements in the quality of experiment write-ups: an IT application can define mandatory fields that the user must complete to close an experiment. In this way it can be guaranteed that fields such as experiment aim or conclusions have been completed.

(3) Harmonisation of experiment write-up format: an IT application, by prompting the user to complete defined fields, standardises the format of experiment write-ups.

(4) Productivity: improvements by automating from the data contained in the electronic laboratory notebook, such as the printing of statistics, activity reports, analysis requests, etc.

The benefits expected from this project and the challenges it raised seemed worthwhile, and thus we decided to set off on this adventure. However, to limit the risks, we chose to conduct the project in a phased manner, permanently in close touch with the end users, and conscious that reaching our goal with this project would be far from easy.

2. Methodology

The application was therefore developed in several phases spread over 4 years. In 1998, technological intelligence gathering and a study of the products already on the market showed that these took insufficient consideration of job-specific aspects and had poor interfacing capabilities with regard to existing in-house systems (molecules databases, reagent databases, LIMS). Conversely, these products were opening the road to our vision of ELN by offering functionalities such as a text editor and a tables editor combined with the possibility for handling chemical structures and reactions. A commercial application was tested for 3 months in a laboratory under real conditions but was found by users to be inadequate.

Aware of the fact that these products, in this form, were unsatisfactory for our use and also that it would be extremely difficult to produce immediately an application satisfactory for most users, we opted to develop first a model, then a prototype (see Figure 1).

This approach, both longer and requiring more financial and human resources, presented a dual advantage. First, it gave the user the means to evaluate the pertinence of the functionalities included in our ELN and to assess the most appropriate method used to develop these functionalities. Second, it provided the users with enough time to accept the idea that they would have to modify their way of working and use an ELN instead of their paper notebooks. Also, this enabled us to show users that this change would not be made at any price, that we counted on developing an application suitable for their needs, and that this application would only be adopted with their consent.

In view of the issues involved in this project and the fact that its development could last for several years, the idea of a project group was rapidly agreed upon. This group was made up of three entities with complementary roles.

(1) A two-man team made up of a users project manager and an IT project manager. The IT project manager was responsible for organisational and IT aspects. The users project manager was responsible for the functional aspects and for project communications, notably with users.

(2) A users group charged with contributing to the establishment of functional specifications and with testing the prototype, different versions, and changes made to the application.

(3) A steering committee charged with taking strategic decisions. This committee was composed of representatives from the job sectors we identified as key players in the development of such an application. This committee included a representative from each of the following departments: scientific information systems, user management, information systems, quality unit, regulatory affairs.

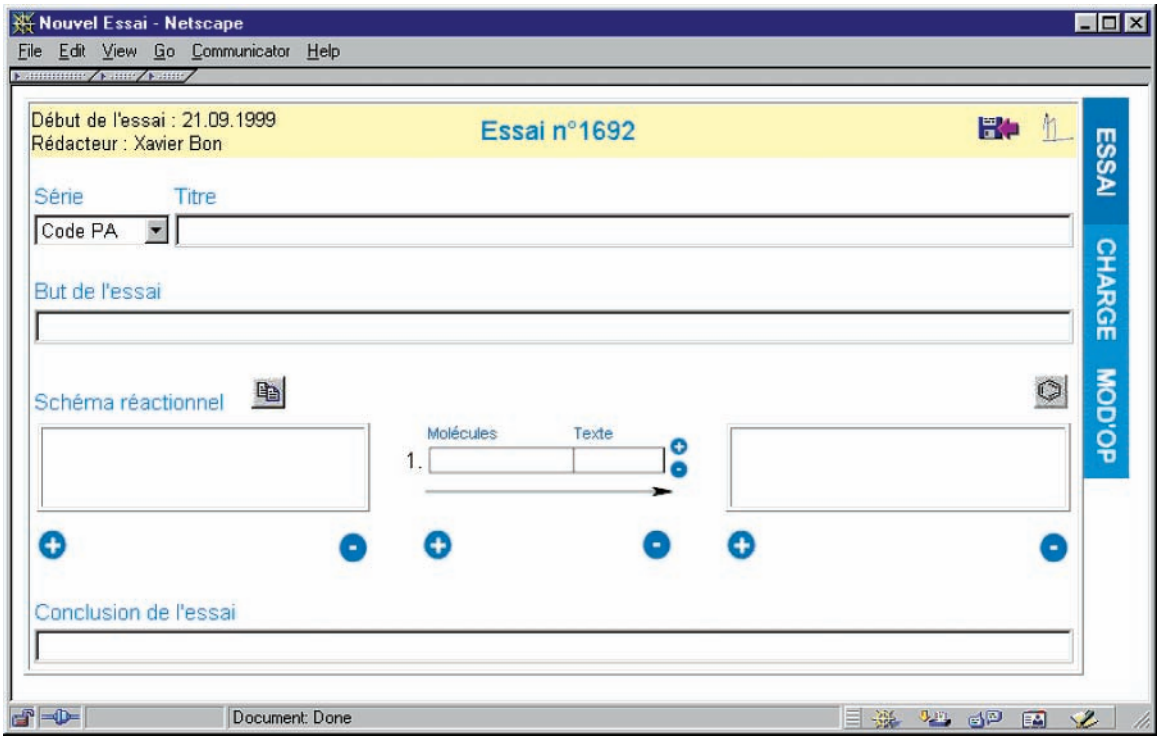

Figure 1. **First screen of the 1999 model (available solely in French).**

The greatest possible transparency was adopted in all the discussions that took place in the course of the project. Minutes were taken at each meeting and were made available to all project players, including the users. We used this approach both for in-house discussions and for discussions with IT contractor teams and thereby established a high level of trust between the different partners involved in the project.

The intention was initially to develop an electronic laboratory notebook application suitable for the different sectors of industrial chemical development. Synthesis chemists working in laboratories were the first to be identified as users. Of these chemists, 80% worked in synthesis optimisation and industrial scale-up of the synthesis, and the processing of non-compliant batches. These laboratory chemists could also be called upon to suggest new operating procedures in the pilot unit for alternative synthesis routes. The reactions on which they worked involved a limited number of molecules, that is those in the Sanofi-Synthelabo portfolio. In this context, the following functionalities were included in the first set of specifications used to produce the LABSTAR prototype:

- construction of reaction schemes from the molecules database used in ICD
- automatic prefilling of the load table with information communicated to the system and describing the compounds used in the reaction
- functionalities used to describe the equipment employed
- automatic calculation of yields
- automatic printing of analysis requests
- access to molecule information pages (structure, names, physicochemical properties, safety sheets), information contained in a corporate database

Our attention at this time focused solely on the job-related aspects of the specifications established for this application. The electronic signature of experiments and the regulatory[1] aspects were deliberately put to one side.

Prototype development was entrusted to the KLEE GROUP, a company with experience in the development of scientific applications for chemists and that had already developed two of our applications in their premises. This prototype, which was intended to validate our choice of the functionalities destined for the final application, made us aware that considerable importance should be placed on ergonomics (the appearance of the display) and the fluidity of display changes when developing such an application. Most user feedback concerned the poor performance of the application in terms of rapidity and the lack of ergonomics which made it more complex to use. This underlined that extreme care must be taken when implementing each functionality so that access is as simple as possible. A few functionalities were added to the specifications on the basis of this user feedback, for example the possibility to copy experiments, to import parts of experiments, to allocate a special colour to the text in the copied or imported parts to lessen the risk of errors, and to open several experiments simultaneously and export the results of a search. We also asked for an experiment validation circuit with electronic signature. Our objective at this stage was not to develop a CFR21 part 11 application since the work conducted in the ICD synthesis laboratories is not subject to audit. Conversely, we were attempting to lay the foundations of an application which, at completion, could be deployed in the analytical

(1) The Collaborative Electronic Notebook Systems Association: an industry body comprising large, predominantly pharmaceutical corporations and software developers. See www.censa.org.

control laboratories that enter into the scope of these regulations. At this point, no functionalities were discarded.

The chemical development synthesis units of course use all the different techniques available when they develop or optimise a new process. Some units work using traditional methods and conventional apparatus while others call on robotics to conduct parallel syntheses or extremely sophisticated equipment for process study and characterisation. Teams work on the synthesis routes or focus on the development of purification techniques which for us are of great importance. We imagined that in view of the great diversity of these different professions, it would be impossible for a single configuration to satisfy all. We therefore decided to draw up a list of specifications focused on the needs of those chemists working with synthesis methods we qualified as traditional. The idea here, if the result proved to be satisfactory, was to define other specifications for the teams specialised in purification or in the use of automated equipment. These new specifications would then be used for future development.

This new set of specifications was reviewed by all the user representatives before being validated. Before proceeding with a new call for tender to develop the final application, KLEE GROUP—which had previously developed the LABSTAR prototype—informed us of its interest in this type of application and its desire to develop a product (Kalabie) on the basis of our specifications. After reflection, we accepted this proposal which appeared to be interesting and constructive for both parties. Sanofi-Synthelabo would benefit from more in-depth developments in terms of product ergonomics and finalisation than it could have financed alone. The fact that we were acquiring a product rather than developing specific software guaranteed that the application would have a longer life-span with the addition, over time, of new functionalities drawn from the needs of other users working in other companies. We were guaranteed the provision of a practically tailor-made application. For its part, KLEE GROUP was guaranteed a contract with ICD and prime positioning with respect to the Sanofi-Synthelabo corporation. They benefited from the experience acquired during development of the prototype and from the feedback provided by our chemists. Their access to the laboratories provided them with the opportunity to see how the application was used in the field, and this feedback enabled them to adjust product development accordingly. Also, KLEE GROUP wished to develop a software package with very flexible settings that could be modulated to fit the needs of different types of users. This allowed us initially to define a traditional synthesis configuration, and if this was successful, to increase the number of configurations to cover other sectors.

Obviously, this alliance also entailed disadvantages since Sanofi-Synthelabo had to agree that some functionalities would not be included in the product, at least in its initial version. At this stage, a detailed study of the specifications was conducted to identify those functionalities to be included in Kalabie, those subject to specific development, and those to be temporarily set to one side for technical reasons or incompatibility with the product's founding principle. The only functionality truly removed from the project at this stage was the colouration of imported or copied zones. Quite logically, the connection with our database, the automated printout of analysis requests, and other functionalities of this type were considered as part of specific product development. The development work started as soon as this study was completed.

The development phase, initially scheduled to last 4 months, in fact took nearly 9 months. This was due to the fact that the application was new and that some of the functionalities included in the product had not been entirely finalised and therefore contained numerous dysfunctions. In most cases, these were only minor, but above all, in view of the time and means deployed for this project, we sought to ensure that the application was favourably received by the users from the very first production version. We decided that since the use of this application would require the chemists to change their working habits, it would enter production only after very rigorous validation. We ensured that all the anomalies identified were corrected before any transfer to production was envisaged. To reach this goal, no less than six versions of the application were tested successively. To obtain the most solid guarantee possible, the application was accepted only after operational qualification (OQ) followed by application testing under real conditions by three chemists in their laboratories for one month (PQ). No distinction was made between the functionalities of the product itself and those resulting from specific development efforts; as a result 600 pages of OQ were drafted accordingly to reach this goal. Despite the laborious nature of the tests and the number of times they had to be repeated, this phase was conducted in a satisfactory manner in so far as the greater the testing effort, the more likely the product was to be favourably received by the users. As far as KLEE GROUP was concerned, despite the delays encountered with respect to the provisional schedule, they continued to improve the quality of their software.

More than 500 points were clarified during the validation phases which in all took four people working full-time 4 months to complete. Once the six successive versions had been fully tested, the final version of the Kalabie application was issued in October 2003.

Over the same period, particular attention was paid to appropriate communications with users who were provided with a detailed user manual and a quick-reference brochure (A4 format) outlining the main functionalities. Half-day training sessions with alternating theoretical and practical sessions were provided to all users and their managers. The aim here was to introduce the users to the application and allow them to become familiar with its function prior to daily use in their laboratories as a replacement for paper notebooks. Two tutors were in charge of six-person groups during these sessions.

Contrary to our initial worries, the users very rapidly became familiar with the application. After only a few hours of practice, all the users—including those with little or no IT skills—were able to use 80% of the functionalities. We found these results greatly encouraging and promising for

subsequent project developments. The application was transferred to production immediately after the training sessions to avoid any breaks. We asked KLEE GROUP for assistance during this phase. The objective once again was to accompany the users, to help them and intervene rapidly if an incident occurred. Some users during this phase chose to place their PCs in the laboratory, whereas others selected the office next door. No major incidents occurred. By contrast, some limitations in the implementation of secondary functionalities had more substantial consequences than initially imagined. Synthesis chemists use thin-layer chromatography (TLC) systematically. These TLC plates needed to be scanned and the image then inserted into the experiment write-up. The Kalabie version 1 image insertion function did not support image dimension changes (unlike Word, for instance) and this rendered the insertion process very laborious: scanning of the TLC plate, insertion of the image file in Kalabie, observation that the image was far too large, removal of the image, search for a more suitable definition, and then re-import of the image into Kalabie. The presence of KLEE GROUP personnel in the field quickly provided alternative solutions, and the development teams were rapidly informed of this point. Version 1.1, available since March 2004, allows the dimensions of inserted images to be altered. Thanks to this active participation, KLEE GROUP modified its product, and the users, while contributing to these changes, benefited from functionalities more suited to their needs.

Once the application was transferred to production for 30 users, our objective was to draw experience from 6 months of use to demonstrate that the application complied with our specifications and with user needs; and this today has been accomplished. During this period the tasks performed by the IT project manager and the user project manager were modified. The user project manager was entrusted with compiling all the upgrades or modifications requested by the users. An exchange document was drawn up for use between the KLEE GROUP and Sanofi-Synthelabo project teams. Sanofi-Synthelabo used this document to note all user requests for changes, and in return KLEE GROUP allocated a status to each. Typical statuses corresponded, to "change implemented in version N+1 or N+2", "must be subject to specific development", "not currently possible". Thanks to this document, which was updated monthly, the KLEE GROUP development teams were made clearly aware of user expectations, and the users were aware of the time frame within which the improvements they requested would be included in the software. This dynamic system provided constant product improvement and was beneficial for both parties.

To ensure that the application was deployed in the laboratories under the best possible conditions, the IT teams made a survey of the space available for PC installation close to laboratory workbenches, network connectors, other PCs, scanners, and printers. These items had been anticipated and had been taken into account in the configuration of new buildings where a large number of power sockets and IT connections had been installed. Thanks to this survey and this forward planning, the PCs installed could be upgraded and extended and scanners and printers ordered. Since the application requires memory space and the installation of Internet Explorer 5 sp2, any PCs not supporting these modifications were replaced. Also, before Kalabie's installation in the laboratories, some PCs were being shared by several users. It was therefore decided to provide each Kalabie user with a PC so that they could use their electronic notebooks in the same manner as their former paper notebooks. In the rare cases where offices were not situated alongside the laboratories, some users were even provided with two PCs. One was placed next to the workbench to record the different operations, the other in their office to finalise the write-up.

Thanks to this organisation, the application was being used spontaneously by all the users one week after its introduction. After 6 months of use by 30 chemists, more than 1300 experiments had been written up using Kalabie and are now available electronically. This success was doubtless due to the fact that we focused on developing a user-friendly application that fitted chemist needs. This vision was shared by both the Sanofi-Synthelabo project team and Kalabie developers. It was inconceivable for us that users would have to make an effort to acquire and use this application.

When deploying the application we decided to cover all the synthesis laboratories. Although the application was very warmly received in those laboratories primarily dedicated to conventional forms of synthesis, more doubts were expressed in the laboratories where robotics are widely employed and in those exclusively devoted to preparative chromatography. In the former, the import of equipment parameters and numerous configuration data was found to be laborious, and in the second the tools we had envisaged for describing the equipment were inappropriate when descriptions for separative techniques were needed, where rather than notions such as reactor type and size it is important to note the type of column and the solvents and gradients used. In this case, certain tabs such as those used to describe the reaction were of little use and therefore proved unsuitable. This feedback confirmed our conviction that if we wished to see the application used by different departments, we would have to define as many dedicated settings as there are job sectors. To do this we drafted appropriate specifications to adapt the application to fit each operating sector.

This project required considerable human resources. In the course of the four years of project conduct more than 20 people were asked to contribute either as users or as members of the IT teams. Development of the Labstar prototype required 2 man-years. The development and deployment of Kalabie took 7 man-years if all the different human resource inputs are grouped together. Kalabie is so far the application used in Sanofi-Synthelabo ICD laboratories that has consumed the greatest amount of human resources.

3. Description of Kalabie Software: "Standard Synthesis" Settings and Principal Functionalities

As required by the functional specifications, "Standard synthesis" settings are similar to those in the paper notebook

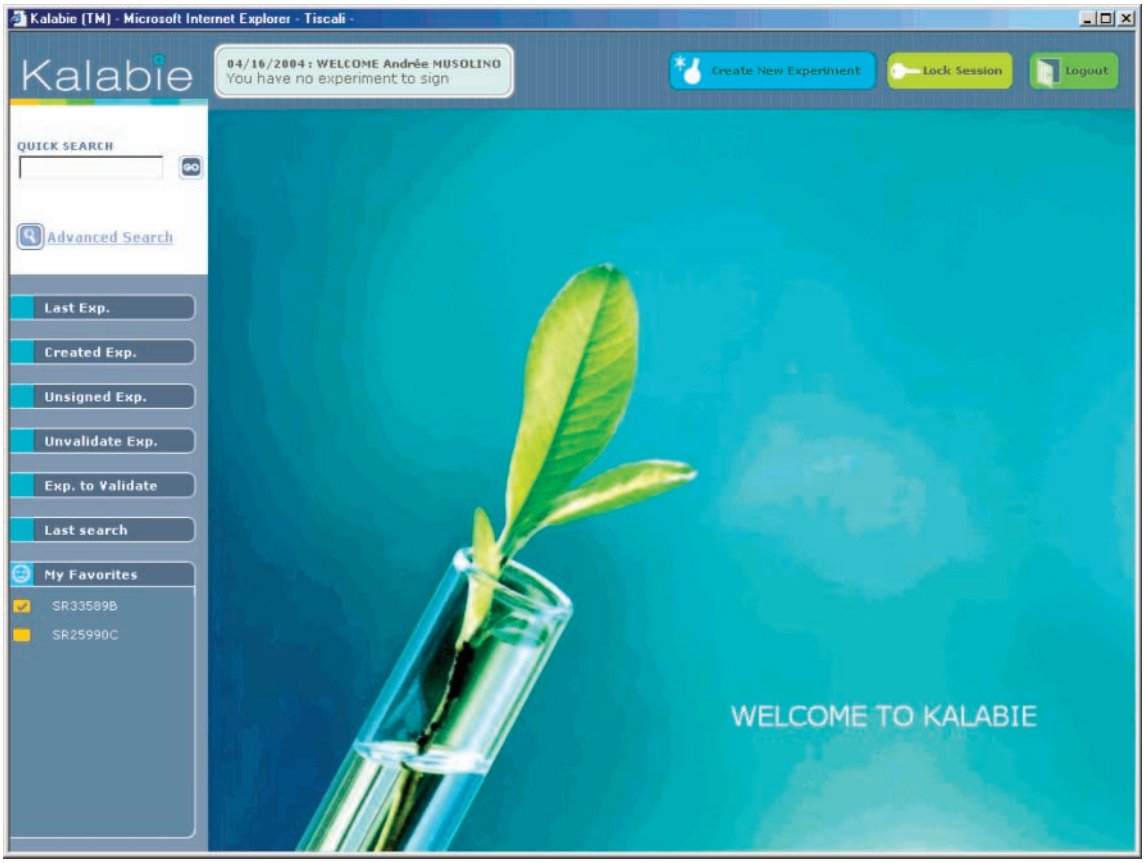

Figure 2. **Kalabie explorer.**

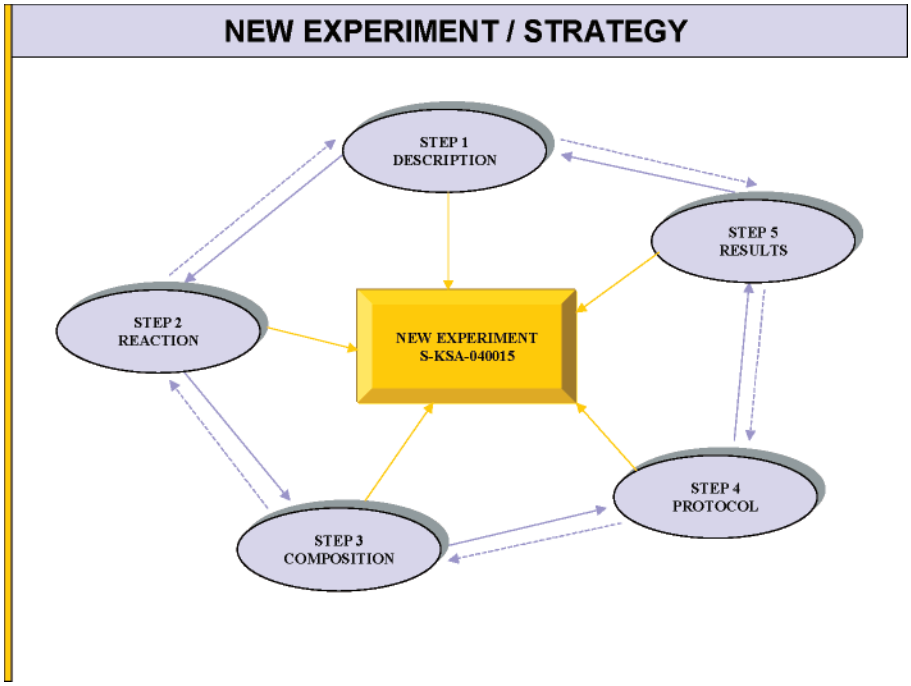

Figure 3. **Experiment design schematic.**

previously used by the chemists. These include sector-related functionalities (experiment creation, consultation, multicriteria searches, search results tables, administration, experiment report, and printing of analysis requests) and general functionalities (access to the application, electronic signature of an experiment, signature and validation circuit, audit file, import, experiment copying and printing, text and reaction editors).

The job-related functionalities include certain specific developments that render the application even more suitable for the direct needs of Sanofi-Synthelabo development chemists. The application interfaces with the in-house Sanofi-

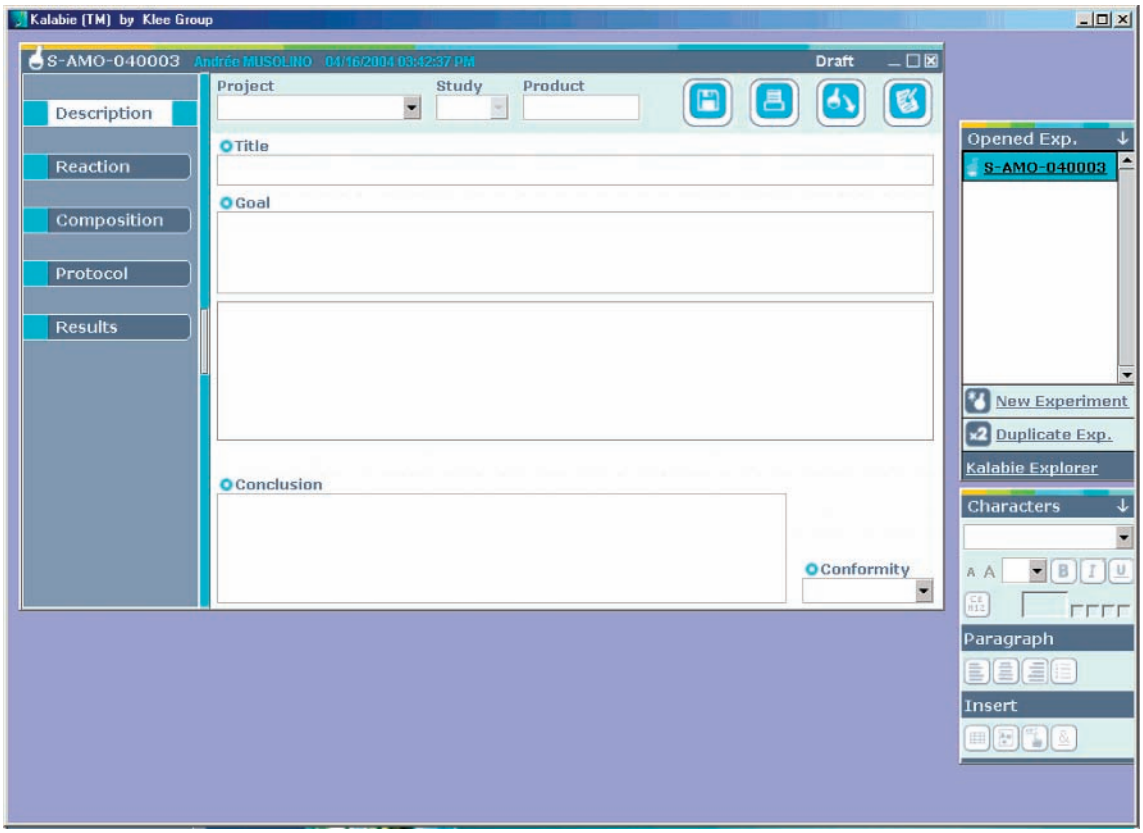

Figure 4. **"Description" window. Definition of experiment title, goal, and conclusion.**

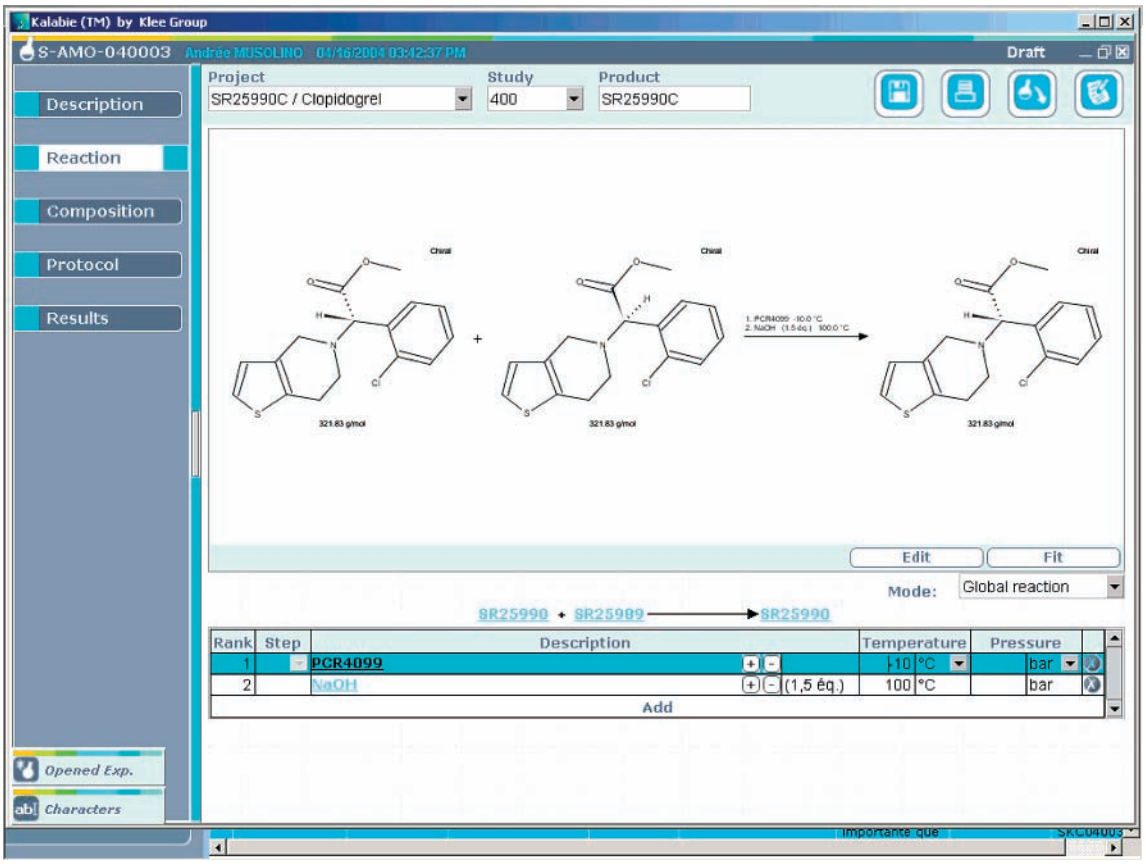

Figure 5. **"Reaction" window. Full presentation of the reaction.**

Synthelabo molecules database and can thus be used to construct reactions and display data associated with reaction compounds (molecule information page). The application includes the notion of multi-step reactions and reaction intermediates and supports the drawing of new molecules using Isis/Draw software. It includes a molecular calculator

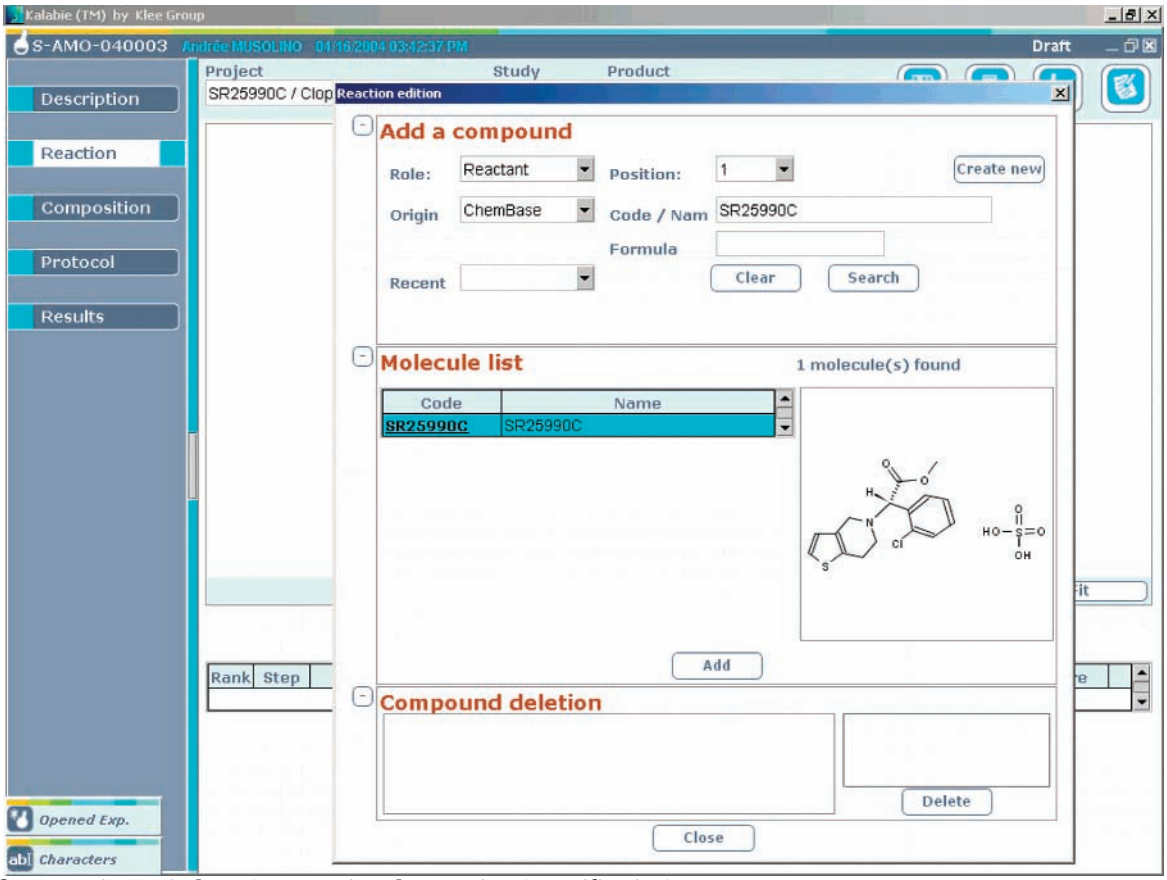

Figure 6. **"Reaction" window. Constructing the reaction (Esterification).**

that automatically completes the load table. This provides the possibility to print experiments and analysis requests in the in-house format. The application also integrates information about the equipment used in the laboratories.

3.1. Connecting to Kalabie. Connecting is easy by using the Internet browser and the address sent by the administrator and by entering the user name and password.

3.2. The Kalabie Explorer. After connecting to Kalabie, the explorer window is displayed for access to the different functionalities available (Figure 2).

This window is accessible at any time during application use.

The menu on the left provides access:

- to quick and advanced search functionalities (described in section...),
- to the last experiment,
- to all experiments already created, by lists of 10,
- to all experiments to be signed off or validated, depending on user status, by lists of 10,
- to experiments meeting the criteria specified in the last search conducted during the session,
- to favourites, which provides the possibility to archive a set of experiments on the basis of a user-defined archive criterion or the experiments resulting from a search, which may be updated.

The bar at the top shows user name, a message concerning experiments to be signed off and three clickable boxes for the creation of a new experiment, session locking, and exit. The central window displays the reaction being edited and the table resulting from a multicriteria search.

3.3. Experiment Editor. An experiment is designed by following the flowchart given in Figure 3.

The different steps correspond to different windows, and the user can switch from one to another at any time while designing the experiment.

3. 3. 1. "Description" Tab. When in the explorer (Figure 2), the user can click on the button "Create New Experiment" to access a window used to select "Standard Synthesis" settings. The user now gains access to the experiment description window and can click on pull-down menus to choose the project and the associated study on which he/she is working, to define product name, experiment title, and goal in rich text format (Figure 4).

The user can also then enter the conclusion (rich text format) and product conformity (pull-down menu).

A frame in this window is reserved for the reaction defined in the next tab.

The four buttons in the top right-hand corner of the window are used to save the experiment, print it out after viewing it in PDF format, or importing and signing the experiment.

The two windows on the right are used to access experiments currently open, create a new experiment, duplicate an experiment, return to the explorer and access text-enriching functionalities and insert special characters, figures, tables, and links to files of different formats. These two windows can be reduced and are accessible from the five "create experiment" tabs.

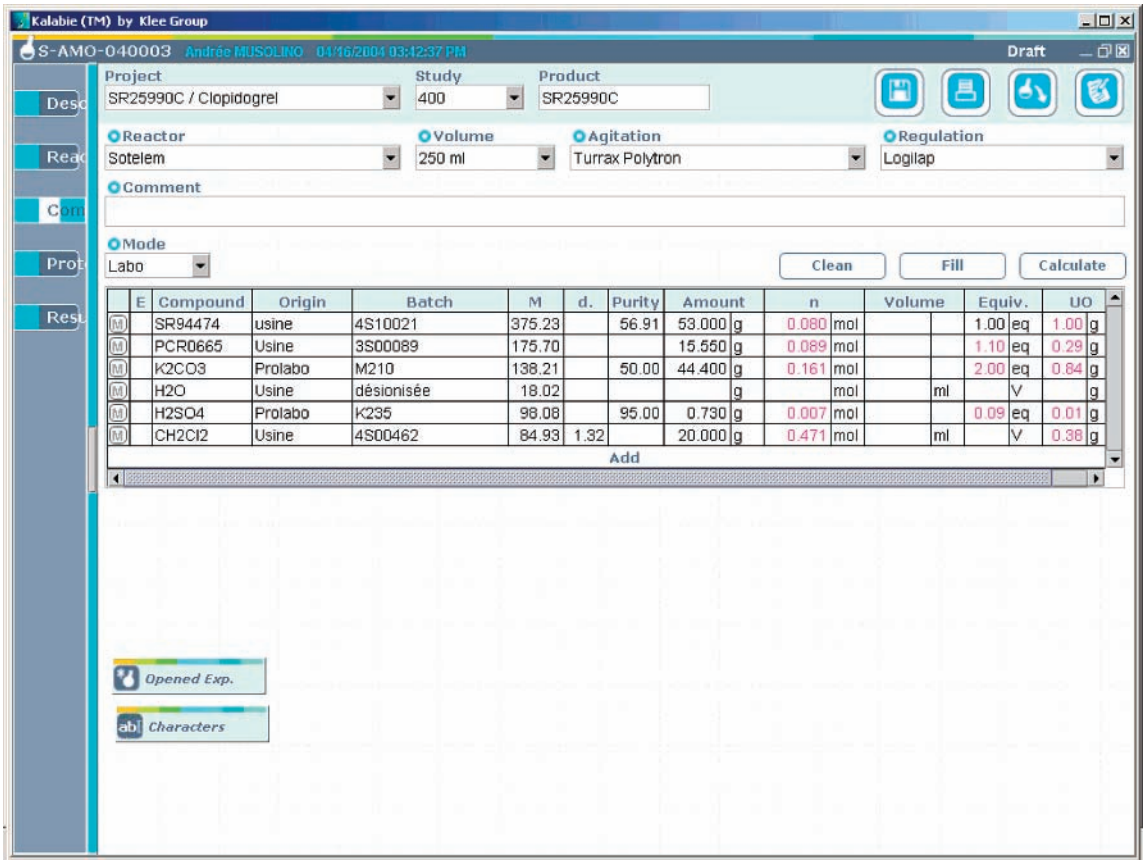

Figure 7. **"Composition" window. Load table.**

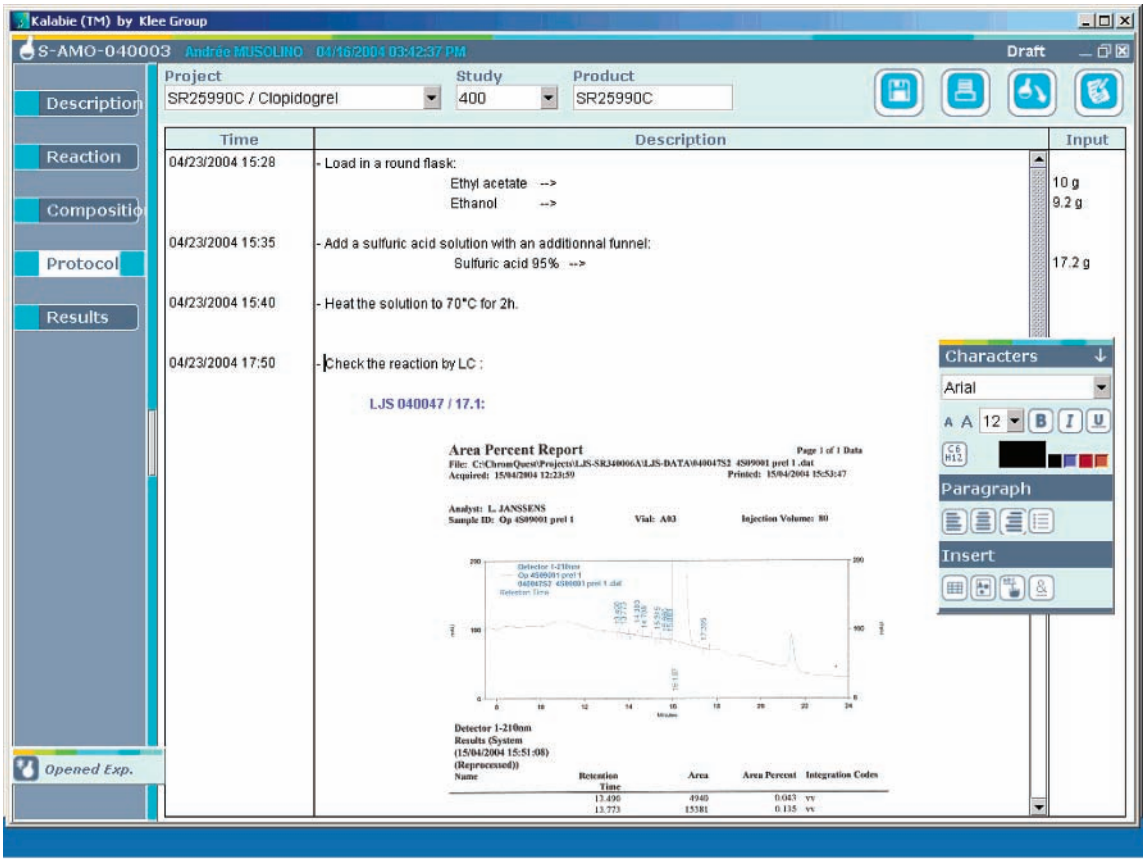

Figure 8. **"Protocol" window. Description of the operating protocol.**

3.3.2. "Reaction" Tab. This is accessible on the left side of the window and allows the user to construct the reaction by interfacing with the in-house Sanofi-Synthelabo ICD database and by integrating the notion of reaction

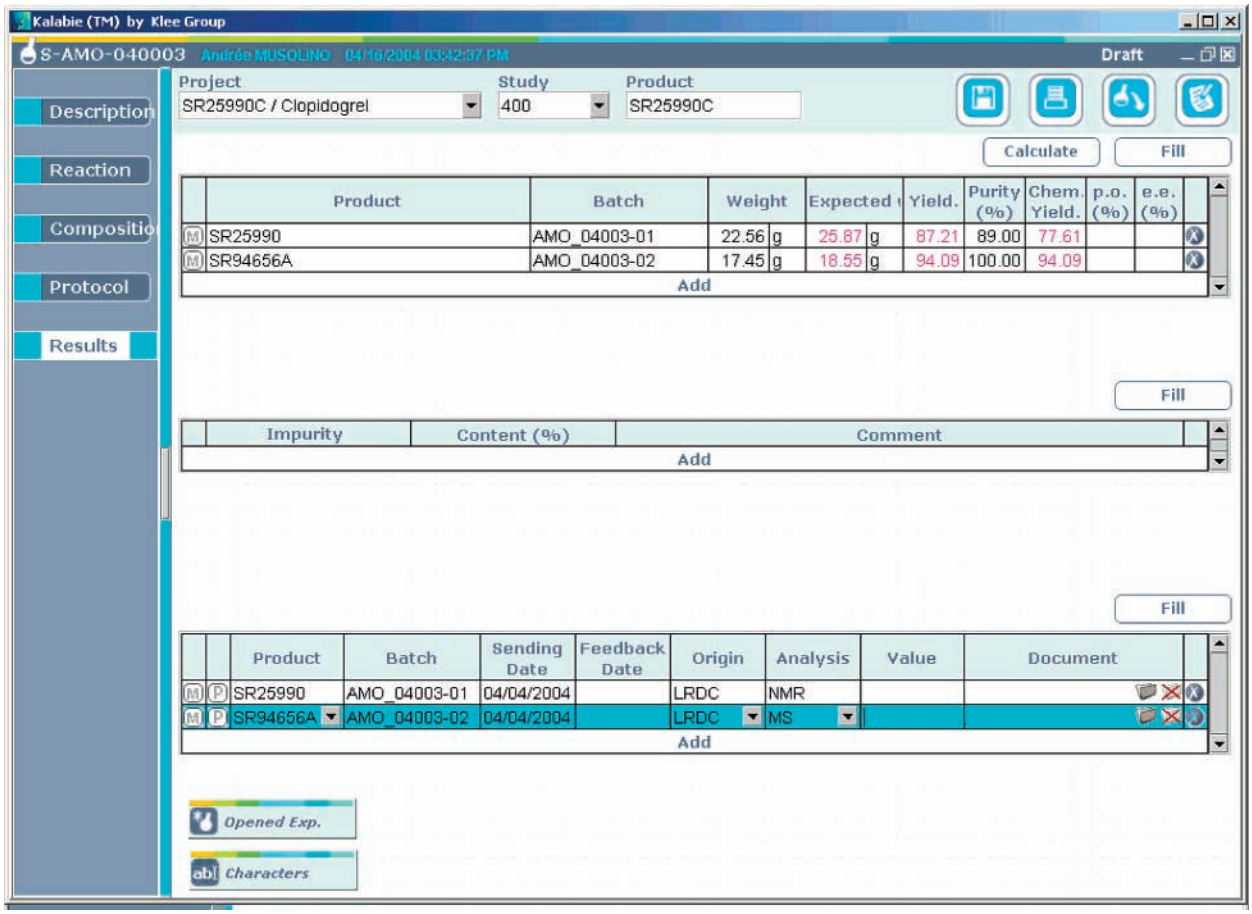

Figure 9. **"Results" window.**

intermediates and multistep reactions.

This part may be seen as customisation that takes into account major job-related aspects developed by KLEE GROUP at Sanofi-Synthelabo's request.

The "Reaction" tab is composed of a central window which shows the reaction (structural representation), after its construction, and the operating conditions (Figure 5).

In the bottom right-hand corner of the reaction frame is a "Mode" pull-down menu used to switch from the complete reaction to intermediate reactions.

A text-based description of the reaction appears above the structural representation and includes updated codes for the molecules involved in the reaction.

The operating conditions are displayed in a table beneath this text.

The molecule codes appearing in the descriptive text or in the table of operating conditions provide access to information pages about the corresponding molecules. These information pages are drawn from the in-house Sanofi-Synthelabo molecules database and include the product's structural formula, references for product safety sheets, names and synonyms and physicochemical properties.

3.3.2.1. Constructing the Reaction. Reactions are constructed from the molecules contained in the in-house ICD molecules database.

Construction starts by clicking on the "Edit" button of the frame reserved for the structural representation of the reaction.

The user must select the compound's role (reactant, intermediate, impurity, product) and its origin (in-house Sanofi-Synthelabo molecules database or Kalabie database) via two pull-down menus.

The user then enters the code, name, or formula for the compound in the corresponding editable fields as partial or total character strings and then starts the search for the compound by clicking on "Search".

A list of the molecules corresponding to the compound sought then appears in the centre of the window. The user selects the compound, checks its structural formula in the frame on the right, and clicks on the "Add" button. The compound then appears in the reaction at the place corresponding to its role. The user repeats this operation until the entire reaction has been constructed (Figure 6).

The user has the option to create a molecule independently of the in-house ICD database by choosing the Kalabie database as the origin of the compound. In such cases an Isis/Draw window appears for the user to draw the molecule, and this is then integrated in the reaction in the same manner as previously.

Once the reaction has been constructed, the user leaves the "Edit reaction" window by clicking on the "Close" button, and the reaction appears in the central frame of the window displayed by clicking on the "Reaction" tab (Figure 5).

The table detailing the operating conditions is constructed in the same manner as the reaction by clicking on the "Add"

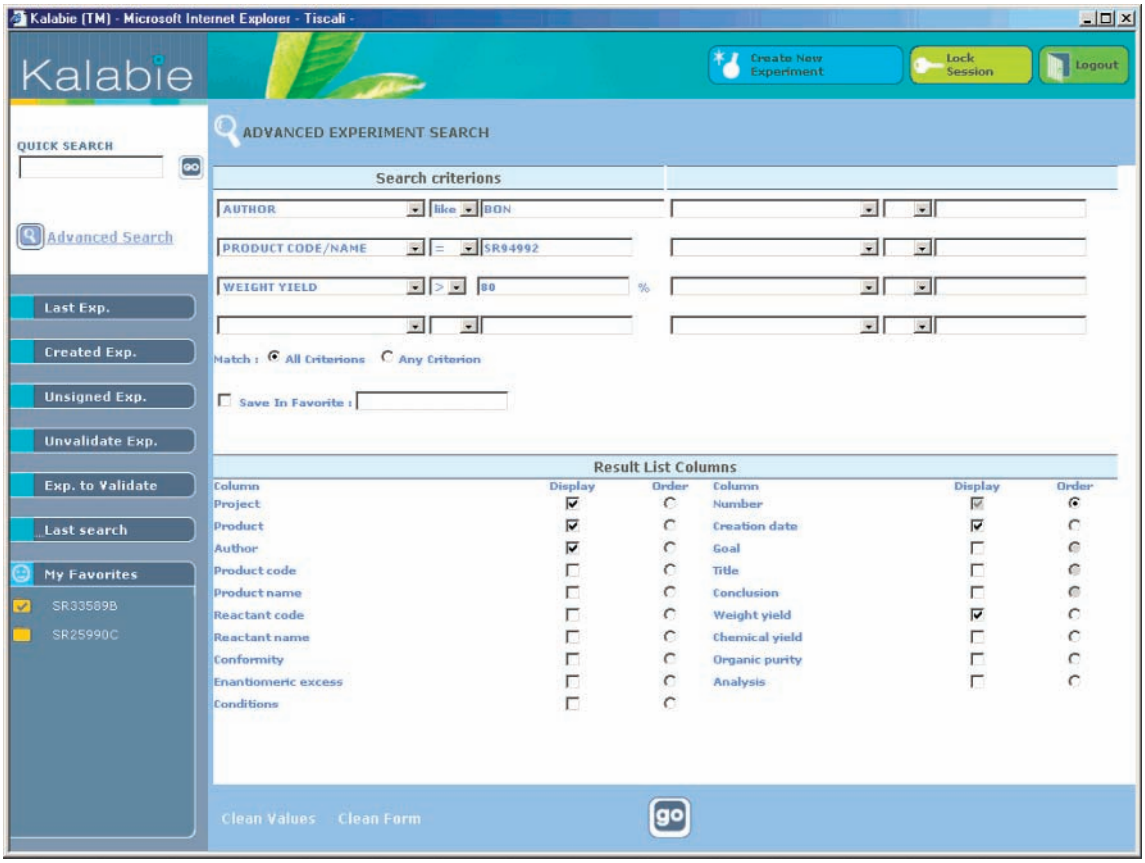

Figure 10. **Defining the critieria of a complex search.**

line of the table then clicking on the + button of the line added. The user is then presented with a window identical to that used to edit the reaction.

The operating conditions appear both in the table of operating conditions and on the reaction arrow.

3.3.2.2. Constructing Intermediate Reactions. This part, requested by Sanofi-Synthelabo, presents the advantage of integrating multistep reactions in a single experiment. This is particularly advantageous when chemists use sequential reactions in a synthesis process. The intermediate reactions are constructed in the same manner as single-step reactions by declaring intermediates in the reaction editor.

The intermediate steps can be displayed via the "mode" pull-down menu in the window resulting from clicking the "Reaction" tab.

3.3.3. "Composition" Tab. This window is used to describe the equipment used in the experiment by selecting in a series of pull-down menus. This tab can also be used to complete automatically or manually a load table for the different species declared in the reaction editor on the basis of certain data provided by the chemist.

The number of moles, the amount, volume, equivalents or operating units can be calculated by two modes: laboratory mode and pilot unit mode. Laboratory mode determines the number of moles for each species employed from the number of moles of a reference compound.

Pilot mode is used to calculate masses and volumes from the mass of a reference compound.

The load table integrates only the species defined in the "Reaction" tab (Figure 7).

3.3.4. "Protocol" Tab. This tab displays a three-column table used to describe the operating protocol followed in the course of the experiment. The first column is used to insert the date and time either automatically or manually. The central column is used to describe the procedure for the experiment using rich text and includes the option to insert images, tables, links, special characters, molecule codes linked to molecule information pages and standard phrases. The last column is used to add the different reaction inputs (Figure 8).

3.3.5. "Results" Tab. This window displays three tables:

- The first corresponds to the results of the chemical reaction itself. For the different reaction products, the mass yields are calculated automatically from the expected masses completed automatically from the load table. Adding the content means that the chemical yield can also be calculated automatically.
- The second table corresponds to the impurities. This is completed manually once the impurities have been imported from the "Reaction" tab.
- The third is the analysis table. This is used to define analysis location and type via two pull-down menus. The values obtained may be entered manually. This table can also be used to print an analysis request on the basis of a template prepared by Sanofi-Synthelabo's industrial chemical development unit. The table can also be used to associate

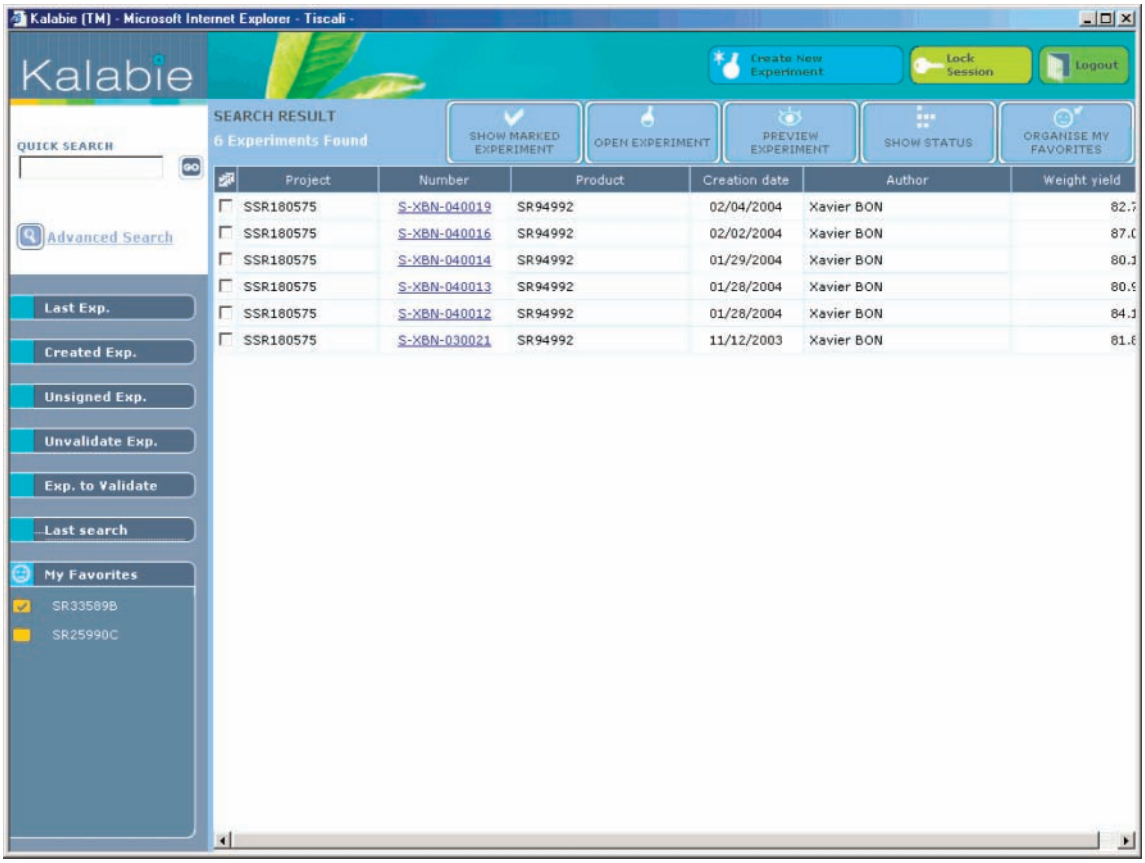

Figure 11. **Table of search results.**

documents in the form of links to a particular analysis (Figure 9).

3.4. Copying and Importing an Experiment. Kalabie's "standard synthesis" settings also include functionalities for copying and importing experiments. Any experiment already entered can be copied either in its entirety or partially. When creating a new experiment, the copied information, i.e., the entire previous experiment or part of the experiment, is imported as the new experiment is constructed.

3.5. Quick and Advanced Searches and Favourites. The quick-and advanced search modules are powerful tools that enable the user to find experiments corresponding to pre-defined search criteria.

The quick search is performed directly from the explorer window by entering the search criterion (or criteria) into the "Quick Search" field in the form of a partial or complete character search string.

The search results appear as a table with defined columns giving the experiments that meet the entered search criterion (or criteria).

An advanced search is launched by clicking on the "Advanced" search link in the Kalabie explorer. This is particularly useful in that it can involve up to eight different search criteria combined by the logic operators "and" or "or".

The search criteria include all the usual parameters employed by chemists (author, aim, reagent code/name, catalyst code/name, product code/name, reactant code/name, impurity code/name, intermediate code/name, solvent name, conclusion character string, conformity, date created, study number, project number, enantiomeric excess, organic purity, mass yield, experiment number, pressure, temperature, type of analysis, analysis value, status (Figure 10).

The table displaying the experiments that meet the defined search criteria can also be modified for the parameters displayed. The experiments can be arranged in relation to a type of result (Figure 11).

Finally, the search results can be archived in a dynamic directory called "Dynamic favorites". Once activated, new experiments that meet the search criteria can be added to this directory over time. When in the advanced search window, the user can manage his or her favourites. In parallel with these dynamic favourites, the user can also create static favourites used solely as a directory for archiving the experiments conducted.

The static and dynamic favourites can be copied, deleted, and renamed.

3.6. Validation Circuit. The validation circuit adopted is composed of two levels: the person writing up the experiment and the witness who validates the experiment. This circuit, accessible via the "Show status" tab in the "Advanced search" window, is used to display experiment status (in writing, in validation, validated, updating). It is the user who makes modifications to his/her experiment. The experiment may be modified even after it has been signed off, on condition that it is then resubmitted to the entire validation process.

3.7. Administration Module. The administration module is used to manage user accounts, signature circuits, the lists

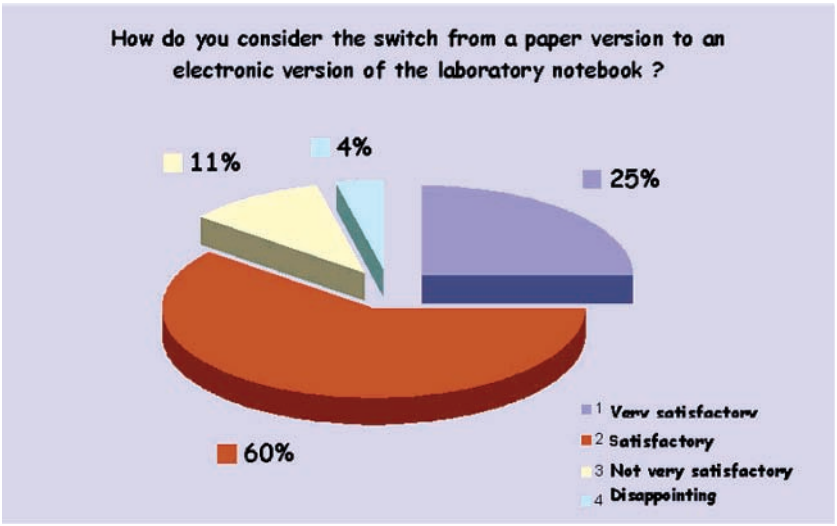

Figure 12. **User replies.**

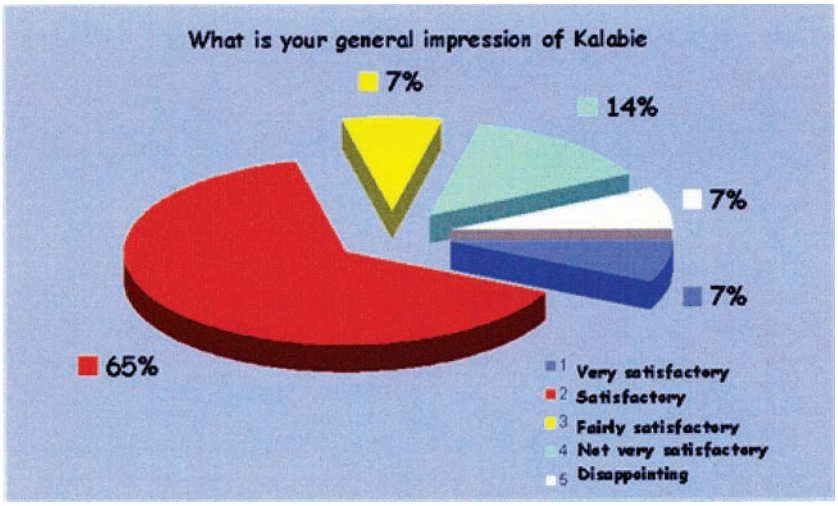

Figure 13. **User replies.**

in the pull-down menus, and integration of new molecules.

4. Overall Results and Key Factors in Kalabie's Success

Kalabie's standard settings proved to be a real success with Sanofi-Synthelabo's industrial chemical development unit in Sisteron and was rapidly adopted by most of the users.

This encouraging result could not have been reached without the project team's determination throughout the development process to remain as close as possible to the needs of Sanofi-Synthelabo development chemists in Sisteron.

The regular involvement of user representatives gradually corrected the deviations observed.

The training support given to users and the hands-on help with which they were provided during initial application use enhanced their confidence and very rapidly supplied answers to their questions.

The fact that their remarks and their requests for changes were compiled constituted further motivation to adopt the application.

The software's user-friendliness and its structure being similar to that of a conventional paper laboratory notebook also facilitated its adoption.

Figures 12, 13, 14, 15, 16, and 17 illustrate user satisfaction on the basis of their replies to a questionnaire.

5. Technical Concepts Overview

Kalabie is an intranet application and this considerably simplifies its deployment, particularly for companies such as ours that possess sites in different countries. The information it contains is therefore shared more easily, and integration with other applications is thereby facilitated.

Kalabie is based on a three-tier architecture:

(1) Oracle RDBMS for the persistence level: Structured data stored in a relational database is more suitable for data analysis and knowledge management purposes. It is also very easy to interface with other corporate Oracle databases.

(2) Java application server: An application server offering connectivity to multiple databases (Scientific, EDMS.). This serves pages for thin client and group communications for all clients.

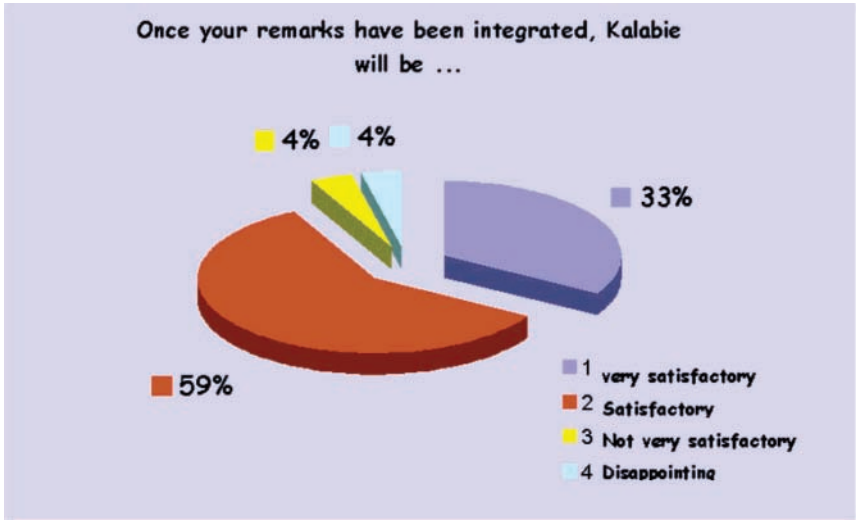

Figure 14. **User replies.**

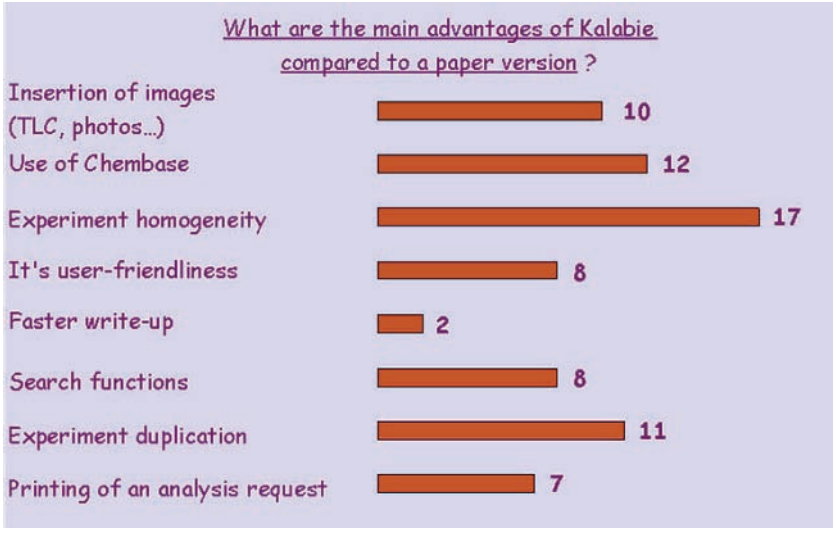

Figure 15. **User replies.**

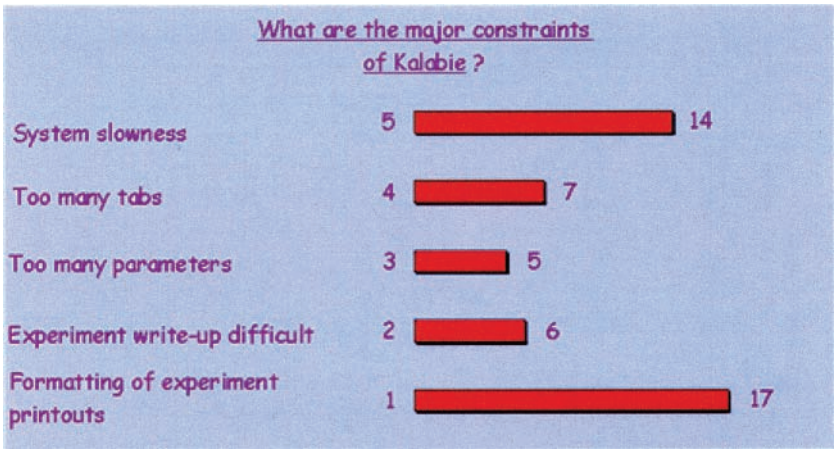

Figure 16. **User replies.**

(3) Intranet-based client: A client divided into two parts: a thin client based on jsp technology for browsing and search functions and a rich client developed with Java technology to create or modify experiments, running on Internet Explorer. The rich client has the advantage of a more user-friendly interface, allowing work on multiple, concurrent experiments and the use of complex components such as text editor or reaction viewer.

An important advantage with Kalabie is that it uses the main open standards on the market, i.e., XML and PDF. Kalabie uses XML for settings and as the native format for experiment handling. This frees us from possible data reading

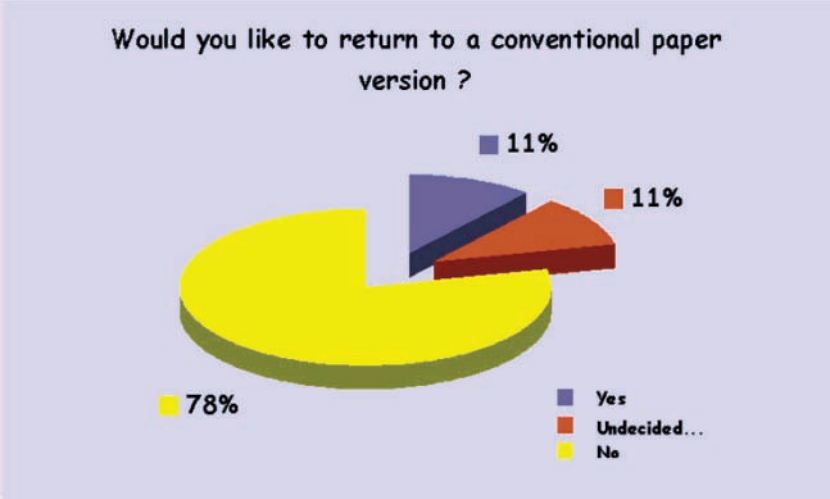

Figure 17. **User replies.**

problems in the distant future, unlike the users of solutions based on proprietary file formats. The experiments are then converted into PDF files that can be printed.

The application is entirely compatible with MDL tools. The molecules and reactions are constructed via the Isis/Draw editor that is launched automatically. The molecules stored in Isis/Host in our corporate database are consulted via the ChimePro plug-in after data import via Isis/Direct.

6. Perspectives

The next step in the project is to implement the user requests for changes not yet integrated by KLEE GROUP into the software. The number of experiment types will be increased to take into account the specific needs of teams performing preparative chromatography and those using automated equipment. The software will also be deployed in analytical laboratories both to report on the work performed by technicians and then to transfer automatically the results of these analyses into LIMS. The advantage of this dual deployment resides in the fact that analysts will henceforth be able to access the reports written by synthesis chemists and thus obtain details about a reaction (reagents, catalysts, solvents, impurities) and the conditions under which it was conducted. For their part, the synthesis chemists will be cognisant of the analytical results as these will automatically be associated with their experiments. Above and beyond the functional aspects, the objective here is to render the application compliant with CFR21, part 11, for future deployment in the quality control analytical laboratories likely to be audited by the FDA.

At the same time, actions will be undertaken from an IT standpoint to determine the most suitable type of computer on the market for entering this type of information: laptops, PCs, terminals, tablet PCs. This study should allow us also to identify the areas near the workbenches where this computer could be installed for the easiest possible data entry. In parallel, an architecture for increased application availability and guaranteeing data conservation should be put into operation. Replacing paper notebooks with electronic notebooks means faultless application availability during the time that work is conducted in the laboratory. The extension of the application for use by all synthesis chemists then to analysis means that powerful machines will be required offering the shortest possible response times.

The decision has been taken to move toward "all electronic" in the medium term in a context where few companies have made the change despite the obvious advantages of ELN.[2]

Acknowledgment

This paper is dedicated to the memory of our former colleague, J. R. Dormoy. This paper would not be complete without thanking those who contributed actively or more indirectly to the success and concrete application of this project. We would therefore like to thank: G. Duc for initiating the preliminary evaluation of electronic laboratory notebooks. L. Janssens, A. Boudin, C. Leroy, and X. Lubeigt for their active contribution to the evaluation and to the testing of the first prototype, LABSTAR. J. R Dormoy, B. Castro for defending and supporting the project. S. Kozlovic, A. Boudin, S. Stoclin, E. Duperron, L. Janssens for testing the first versions of Kalabie. R. Manwaring, P. Belin, J. Espejo, G. Ricci and P. Mackiewicz, and B. Castro for assisting the project team in bringing the project to fruition. A. Ramet for supporting and financing the project. M. Garde for assistance in the drafting of the specifications. C. Abello, S. Rolland, E. Martin, G. Moullet for IT support and J. Leroux for assisting users in the interface with the ICD molecules database. F. Beillouin (KLEE GROUP) and his team for their proactive approach and their availability throughout the project.

Note Added after ASAP Publication: In the version published on the Internet October 5, 2004, there were minor errors in formatting and errors in the numbering of the advantages listed on the second page. The final version, published October 14, 2004, and the print version are correct.

Received for review May 20, 2004.

OP040012V

(2) Bruce, S. *Scientific Computing and Instrumentation*; Reed Business Information (Reed Elsevier): France, January 2003; Vol. 20, No. 2, pp C-15−C-19.