AUTOMATED MANAGEMENT OF THE REGULATORY ASPECTS OF THE DEVELOPMENT AND
REGISTRATION OF PHARMACEUTICAL PRODUCTS

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Regulatory Affairs - International (RA-I), Merck Sharp & Dohme Research Laboratories, Merck &
Co., Inc. is active in the administrative aspects of planning, obtaining clinical study
authorizations, conducting clinical drug trials and the international registration of new
pharmaceutical products. The past decade has seen an increased interest in Good Clinical
Practices with heavy emphasis being placed on the documentation of all aspects of clinical
studies. As communications between worldwide regulatory agencies and the number of studies
conducted by Merck have increased, the ability to respond in a timely, efficient and effective
manner to regulatory questions and requirements that continue to grow in number and complexity
has become mandatory. To meet this need RA-I developed an automated integrated information
system.

Prior to the development of the system, each area within RA-I maintained numerous handwritten
logs containing administrative information from documents received in the department. These
logs were used to document the development of each clinical program. As a program is planned
information is gathered on the number and types of studies to be conducted, and target dates are
set for each step necessary to conduct the studies, process the data, summarize the
results and file for registration. Protocols are then written for each type of study to be
conducted and clinical supplies are manufactured and packaged according to the protocol
guidelines. As investigators are solicited to conduct a study, a signed protocol along with a
statement of education and experience is obtained and clinical supplies shipped to the
investigator. Patient data captured on case report forms is received in the home office and the
information contained on the forms is entered into the clinical data base. Special adverse
experience report forms also are received and recorded for every adverse experience encountered in the studies. When the studies are complete or sufficient data have been received in accordance with the projected target dates, the data are summarized and reports written for each protocol. These Clinical Study Reports are then summarized in a Clinical Experience Report (CER) which, along with the
Basic Data File (chemical and pharmaceutical information on the compound) and Preclinical
Evaluation Report, is submitted to regulatory agencies worldwide to obtain registration approval.

The myriad of documents generated by the process just described fall into 10 basic categories:
program status; protocols; clinical supplies; study related data; patient related information;
adverse experiences; study summaries; quality assurance of data; clinical study
authorizations (CSA) and registration information; and questions raised by regulatory agencies.
Likewise, the major responsibilities of the RA-I Staff are separated into the same 10
categories with handwritten logs maintained for each category. In automating the logs, it was
apparent that many contained identical data causing unnecessary duplication of work. The
new system referred to as the International Registration Information System (IRIS), was
developed to prevent this duplication of effort through the use of common identifiers which also
made possible the merging of all information to produce comprehensive management reports.
The use of common identifiers also assures consistency in the recording of information by
all groups.

IRIS consists of 10 separate subunits which correspond to the categories previously
described. Each subunit is maintained independently by one individual. As documents are
received in RA-I the administrative information from the document—such as the date of the
document, date received in the home office and date of approval—is registered directly into
IRIS by the person responsible eliminating the need for handwritten logs. The following are
eXamples of the type of information recorded in each subunit.

Program Status

Number of studies and patients planned for each protocol to be conducted in the program

Target dates for each protocol for:

- protocol approvals
- ordering of the supplies
- initiation of the study
- receipt of the last case report form
- approval of the statistical analyses
- approval of the study summaries

Target dates for the program for:

- release of the registration documents
- registration approval

Protocol Information

Program identification number
Complete title
Date drafted
Date approved
Date released
Area generating the protocol (individual
country or home office)
Area approving the protocol
Clinical Supplies

Documents requesting manufacture and packaging of drug:
- originator’s initials
- date
- approval
- drug name, potency, quantity and identification number

Documents requesting shipment of drug:
- originator’s initials
- date
- country drug shipped to
- acknowledgement of receipt
- distribution of drug to investigator
- return of unused drug

Study Documents

Signature date on protocol
Approval of signed protocol
Date of receipt of:
- statement of experience and education (curriculum vitae)
- normal laboratory values form
- non-IND form
- publications
- statistical analysis
- letters
- Investigator identification number

Patient Data

Patient demographic information
Dates of receipt of:
- case report forms, by period
- work sheets
- adverse experience forms
- quality assurance queries
- letters, telexes, etc.

Adverse Experiences

Drug name
Seriousness of adverse experience
Adverse experience common terminology
Date sent to domestic headquarters
Date sent to the U.S. Food & Drug Administration

Study Summaries

Type of summary—individual, multiclinic, overall program
Date summary:
- received for typing
- placed in the review cycle
- approved for release
- released by RA-1

Quality Assurance of Data

All documents received prior to cut-off date
Questions raised and resolution
Type of audit conducted i.e., raw data vs computer data base or raw data vs study summary
Name of auditor
Date audit completed

Quality Assurance of Data (Cont.)

Location of original documents

CSA/Registration Documents

Drug number
Date & title for each:
- Basic Data File
- Preclinical Evaluation Report
- Clinical Pharmacology Report
- Clinical Experience Report
- International Physicians Circular
- Legalized Documents

Drug Samples
Country each document sent to
Initials of person receiving document
Date of receipt in each individual country
Date information was filed for registration
Date registration was obtained

Regulatory Queries

Drug number
Exact question raised by each regulatory agency upon review of the registration dossier
Date question received in headquarters
Date the answer was sent to the individual country for response to the agency
Document used to answer the question
Target date for answering question if additional data is required

After the content and format of all subunits were determined, each subunit was implemented through an IBM 3278 terminal linked to an IBM 370-168 computer. All logs are comprised of three types of data sets stored on a dedicated 3350 disc pack: raw data, SAS programs and a SAS data set.

The "Raw Data" data set contains the actual data entered into the system by RA-1 personnel. Password protected data sets (of 72 columns) are used which are formatted with headers to facilitate the entry of variable information via IBM's Structured Programming Facility (SPF). The individual responsible for the accuracy of the information enters the information through the terminal directly in the "Raw Data" data set, thus eliminating the need for handwritten logs. Currently there are over 165 "Raw Data" data sets. Formatted header information as defined in the actual data set contains abbreviations to reduce space requirements. The user keys in only the variable information.

Three types of SAS programs are used for each log: programs that read the raw data and create SAS data sets, programs that produce standard basic reports and programs that produce special reports or queries. Storage of the programs on disc allows the user to obtain any report by simply executing a TSO "SUBMIT" command for background job execution which prints the reports on an IBM 3800 high speed laser printer.
It is also possible to execute the program online if an immediate answer is required.

The information from all logs is stored in one SAS data set which currently occupies 200 tracks and can also be accessed by other departments within Merck by request. A modification of the Proc Contents procedure is used extensively to insure consistency in SAS variable names and definitions.

The system was designed to eliminate duplication of data entry and to contain common identifiers in each log which enable comprehensive management reports to be readily produced using information entered on a daily basis. For example, the Program Status Report contains: target dates from the Program Projection Log; generic protocol titles and approval dates from the Protocol Log; information concerning receipt of supplies from the Clinical Supplies Log; receipt of signed protocols and case report forms from the Document and Patient Registry Logs; and shipment of the Basic Data Files, Preclinical Evaluations Reports, Registration Samples and the date of registration from the Registration Log.

The flexibility of SAS report writing procedures allows for special reports to be easily obtained. In many cases the same information is required by several individuals, but each individual requires a different ordering of the data. These requests are completed quickly by a simple computer sorting change, eliminating time consuming hand tabulations. Standard and special queries that enable RA-I to verify that good clinical practice guidelines are being adhered to are becoming an easier and more efficient task using the capabilities of SAS.

In summary, IRIS is an interactive system that enables RA-I to quickly respond to questions raised either by other departments within Merck & Co., Inc., or regulatory agencies, concerning the status of any document(s) that has been received in Regulatory Affairs - International. SAS has enabled RA-I to design, implement and maintain this system with minimal support from Systems and Programming.