Metabase

Security, Quality Assurance, GLP, and GALP Features

Metabase is a software application based on Microsoft Excel.™ The program provides data collection, management, analysis and reporting functions for metabolism and pharmacokinetics studies, and is custom designed to integrate with radioanalytical instrumentation and procedures used in a typical metabolism laboratory. The program is designed for use in a GLP-regulated environment. Complete validation (system life-cycle) documentation and a verification test procedure are supplied with each custom application.

The purpose of this document is to describe the security, Quality Assurance, GLP, and GALP features and options associated with the use of Metabase. Excel provides a number of options for securing workbook information from unauthorized use and for protecting workbook data and items from changes. Some of these are used by Metabase, and others could be adopted and applied as part of your laboratory's Standard Operating Procedures. Additionally, Metabase incorporates several design features specifically intended to safeguard acquired data and eliminate avenues for unintentional changes. The various data security and protection options which are either available as Excel functions or are built into Metabase are itemized in the following sections.

Summit Research will work closely with your QA, computer validation committee, and end-users to insure that Metabase meets your security, compliance, and validation needs.

■ Excel Security Functions

File Protection

For higher level security, Excel provides three options to limit file access and changes. These may be incorporated in Standard Operating Procedures pertaining to the use of Metabase or its associated programs. These options can be applied at any time using the Option feature in the Save As dialog box. The options are listed in the order of increasing security as follows. First, the user can have Excel recommend that Metabase, or any of its workbooks, be opened as *read-only*. When the file is first opened, the recommendation can be accepted or declined. If accepted, then any changes made can only be saved by creating a new file. The original file remains intact without alteration. On the other hand, if the recommendation is declined, then the user has full read and write privileges and any changes made become permanent when the file is saved.

The second level of security is called *write reservation* and requires a password to save changes made in the workbook. If the user does not supply the password, then the file can only be opened as a read-only file; no changes can be saved to the original, although a new file containing the changes can be created.

The third level of security involves assigning a password in order to open Metabase or an associated file. Password protection can be combined with read-only and write reservation protection.

Cell and Objects Protection

Every cell on a worksheet can be formatted as either locked or unlocked. A locked cell cannot be changed, deleted, moved, or copied over. Other worksheet objects, such as text boxes,

drawing objects, and control buttons can be similarly protected. By default, all cells and objects are formatted as locked and visible, but this feature is applied only when protection for the worksheet is activated. Protection can be activated or deactivated for individual worksheets at any time by the user. For added security, a password can be required to prevent unauthorized turning off a worksheet's protection feature. Metabase routinely hides its VBA modules, and these may be given password protection by the user. Use of cell and object protection can be applied, but locked objects must be programmatically unlocked to allow macro-based writing to cells. Metabase relies on the carefully programmed movement of data into, within, and between worksheets. Much of the data exchange within Metabase is dynamic in nature, with databases expanding as data is added and fields adjusting their values to reflect changes in linked cells. Coding to allow for macro-controlled cell changes in such a dynamic environment is not always the most practical approach for maintaining data integrity. Cell, object, and sheet protection can be applied for specific work areas; however, Metabase also incorporates a number of other features designed specifically to insure and verify the integrity of data.

Code Protection

Metabase uses Visual Basic for Application as the operating code. The code modules can be password protected from alteration or permanently hidden from view and any access. Additionally, Metabase can be custom programmed to meet specific security needs. For example, administrative authority can be given to a single user who, in turn, can enter user access information such as password and user identification, which is recognized when the user logs in.

■ QA Design Features

Template Files

Metabase is supplied as an Excel template file, which is the basic document containing all the features, functions, formulas, formats, and Visual Basic modules that make up the program. The original Metabase template is the program file that is actually used for validation and testing. The template is available as a read-only file and a copy of the template is made each time Metabase is opened to create a new study file. Thus, in combination with periodic maintenance testing, the use of a validated template ensures that each working copy inherits the same validation status as the original template. The Metabase template is given a version number and date that are passed to all copies. Improvements or changes to the Metabase template are governed by documented change procedures that are traceable through these version numbers and dates.

Automated Data Acquisition

Metabase is specifically designed to automate data acquisition and eliminate any hand-entry of instrumental data. The two types of initial data that are used by Metabase are sample processing measurements (weights or volumes) and liquid scintillation counting (LSC) results. Quantitative data can be obtained from automated bench-top balances or robot-controlled balances. All data is accumulated in a specially designed spreadsheet (Sample Processing Form) with audit trails and a built-in safeguard against overwrites. Metabase automatically checks to insure that imported data files have the same Study Number.

LSC data is simultaneously printed as a hardcopy output (to be retained as raw data) and written to a diskette as an ASCII file or transferred to an interim file via the RS-232 port. Metabase provides user-controlled automated procedures to open, read and transfer ASCII file data while locking out any possibility of changing the original file.

Data Verification

Metabase maintains two separate databases which serve to collect, composite, and store incoming data derived either from the quantitative weight measurements and the LSC results. User controls are provided to transfer data from these two databases to the master Radio-Analytical Database (RADB), where all calculations are performed and from which study printouts are made. This scheme provides a ready means for comparing the input data with the output data in order to verify that they are identical.

Add-Only Database Design

The master database in Metabase is the Radio-Analytical Database (RADB). The RADB collates sample information with weight and LSC data, performs all required calculations, and serves as the source for study printouts. One of the data integrity measures built into the design of Metabase is the use of RADB as an add-only file. The RADB is the main collection point for study information and is assembled and manipulated entirely through VBA procedures. Information is transferred to the database using automated procedures, but there are no provisions for removing data. The intent is that all data produced by the study are retained within the RADB, including results from samples that are repeated or reprocessed. Sample results can be sorted to segregate repeated assays, but all results, whether used or not, are retained in the RADB.

Non-Overwrite Provision and Database Audit Logs

In keeping with its add-only design, the RADB is programmed not to allow overwrites during the transfer of sample weight and LSC data. All incoming data transfers are done by a merging procedure. Although resident data fields (cells) are initially blank and serve only as placeholders for incoming data, each place-holder cell is examined to insure that it is blank prior to completing the data merge. If data is detected in a placeholder, then the merge does not occur. Instead, both the incoming and resident records are retained in the database and flagged as duplicates for user attention. A copy of both records is automatically placed in the Audit Log sheet and date stamped. This is a pro-active approach which prevents any overwrites from occurring within the master database. The safeguard is redundant since the database fields are initially blank, but it is built into the program to actively prevent any inadvertent overwriting.

Similarly, external Sample Processing Form workbooks, which are deployed in the laboratory for connection to balances, also have active internal protection against inadvertent overwriting of data. Should the user allow overwriting (e.g., to repeat a weighing), the program automatically records the entire record to an Audit Log before proceeding.

Formula and Calculation Protection

Metabase makes extensive use of formulas and special VBA functions to locate data used in calculations and to compute results. Although Excel provides the means for hiding formulas so that they do not appear in the entry bar when the cell is selected, this feature is not used because the user's awareness of formulas is an important aspect of understanding the

program's function. Furthermore, the program is designed to prevent corruption of data by inadvertent or direct alteration of formulas. This design has two parts. First, all formulas are derived from VBA procedures which control the writing and placement of formulas in cells. This feature insures that all calculations are based on original, tested, built-in formulas that can be refreshed at any time through automatic or user-directed macro operations. The module sheets that contain the formula code are hidden from the user and are actively protected against change or alteration. The second design feature for preventing formula-related data corruption is the routine freezing or fixing of results obtained from formulas after the formulas are applied. For the most part, this is accomplished automatically in the process of writing and applying formulas. The main database (RADB) provides the user with button options for both calculating results (applying formulas) and freezing the calculated results as values. The user can recalculate and fix data at any time.

Link Protection

Linking one cell to another in order to share or acquire information is a powerful Excel capability used extensively by Metabase. However, Metabase programming applies a number of strategies to avoid potential problems associated with linking. First, Metabase is designed to be a self-contained program and does not maintain or depend upon links with any external workbooks. This approach avoids the confusion and difficulty associated with maintaining links to external files that may be moved, renamed, or copied. It also limits the number of files requiring surveillance and protection. Second, Metabase links are all formula-based and are primarily used to look up data in adjacent worksheets. The freezing of formula-based data, as described above, safeguards against altering calculated results due to inadvertent changes in remote, linked cells. In sum, although Metabase uses links extensively, all links are self-contained and are designed to close when not in use.

■ Application of GALP Guidelines to Metabase

EPA's Good Automated Laboratory Practices (GALPs) is a uniform set of procedures issued to assure that all Laboratory Information Management Systems (LIMS) data used by EPA are reliable and credible.[1] The GALPs include many of the requirements of Good Laboratory Practice (GLP) Standards[2] for managing the conduct of studies. Not all automated laboratory systems are subject to GALP requirements. The criterion used in the GALP guidelines to define a regulated system (referred to as a LIMS) is the ability to effect changes to original observations or measurements. Thus, if data entering automated laboratory systems can be manipulated or changed in any way by the action of a person prior to being recorded, then that automated laboratory system is a LIMS.

Whether or not Metabase fits the definition of a LIMS, as given in the GALP guidelines, depends on when instrumental data is first recorded in relation to its use by Metabase. In the case of liquid scintillation counting (LSC), the instrument usually produces data and records it automatically on a hard copy printout. This is the raw data output. The data transferred to Metabase is a virtual electronic copy of the raw data (either as an ASCII file or RS-232 data feed) and is captured after it is recorded. Since a person prior to recording cannot alter the data, the LSC data input to Metabase does not technically constitute a regulated LIMS interaction.

Automated weight measurements used by Metabase can derive from two sources: robotic weighing systems and automated balances. Robotic procedures record and store original weight results in a local data system. After the data is recorded, a copy of the data is passed to a separate file or directly incorporated into Metabase's Sample Processing Form workbook on

a separate computer (or hard drive) established for this purpose. In this case, the original record is retained in or printed by the robotic system and cannot be altered by a person. Thus, neither the robot subsystem nor the Metabase interface meets the criterion of a LIMS. Similarly, automated laboratory balances can be configured to produce an independent raw data printout or ASCII. Since either configuration prevents altering the data before it is recorded, neither approach falls under the definition of a regulated LIMS.

Metabase is designed to be an independent data management program that does not acquire raw data per se during its automation processes. Data inputs come only from previously recorded sources. Even the Excel form used to acquire weight data is external to Metabase. Therefore, GALPs are not strictly applicable to the use and operation of the program. Nevertheless, since Metabase functions in regulated laboratory environments, since it involves the processing and managing of data, and since the practices and procedures for safeguarding the integrity of data are a priority concern, it is Summit Research Services (SRS) policy to design, document, validate and test Metabase in conformance with applicable GALP guidelines. Like GLP, the GALP guidelines are viewed as good practices, even if they are not required in all respects. SRS provides full support to assist client laboratory management and Quality Assurance Unit personnel in meeting all applicable regulatory guidelines and requirements for LIMS and data management systems.

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[1] *Good Automated Laboratory Practices: Principles and Guidance to Regulations For Ensuring Data Integrity In Automated Laboratory Operations with Implementation Guidance* (August 10, 1995) 1995 Edition. Scientific Systems Staff, Office of Information Management, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711.

[2] *Good Laboratory Practice Standards.* 40 CFR Part 160. Federal Register Vol. 54, No. 158, August 17, 1989.

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