

Addressing the need for a Highly Automated LIMS for In Vitro ADME/Tox

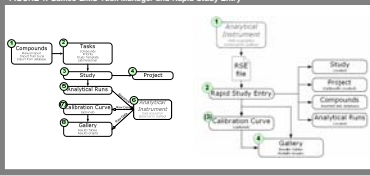
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Introduction

- ADME/Tox profiling has become increasingly important for efficient drug candidate selection and optimization of a compound's physicochemical properties
- Large numbers of compounds and a wide variety of in vitro ADME/Tox screening assays and methods are employed at an increasingly faster pace. This has resulted in ADME/Tox profiling becoming a bottleneck in the drug discovery pipeline
- Point solutions, such as standalone spreadsheet and graphing tools, are inefficient, prone to errors and lead to inconsistent results. Template modifications propagated over time lead to variations in data handling and problematic "apples to apples" comparisons.
- The lack of a central repository results in data scattered in disparate locations (i.e. individual users' hard drives) without traceability
- Data management systems can reduce effort and manpower required and increase throughput by automating complex experiment templating, instrument interfacing, data analysis, review and acceptance tasks
- Thermo Galileo LIMS™ is an integrated informatics solution that is designed specifically for in vitro ADME/Tox profiling
- Study design templates allow specification of key experimental variables such as drug and inhibitor concentrations, species, biomatrix, tissue, analytical time points, and assay method, result calculation options, etc
- LC-MS data (or other instrumental data) can be imported via Rapid Study Entry (RSE, Figure 1) using a simple dialog (Figure 2). RSE creates new studies and projects on-the-fly and populates the template's design with study data

FIGURE 1. Galileo LIMS Task Manager and Rapid Study Entry



Rapid Study Entry Workflow

The RSE process in Galileo LIMS (Figure 1) rapidly transforms analytical data into in vitro ADME calculations and graphics:

- Analytical instrument data is acquired and converted into a Microsoft Excel®-based RSE formatted file
- During data import the RSE function (Figure 2) allows for:
 - Assignment of study design templates
 - Insertion of new compounds into the database
 - Creation of analytical runs
- Optionally, calibration curves may be processed using various regression algorithms to convert peak areas into concentration values e.g., for IC50 or Ki studies
 - This step is not employed if peak area data is used directly for in vitro ADME calculations; for example metabolic stability.
- The Gallery provides rapid data review in multiple formats

FIGURE 2. Galileo LIMS Rapid Study Entry Dialog



FIGURE 3. Galileo LIMS Gallery Tabular View of Metabolic Stability Data with Results Flagging



Gallery-Based Data Review

- The Gallery presents data in tabular (Figure 3) thumbnail (Figure 4) or detailed (Figure 5) views
- The thumbnail view allows user to scan quickly across many datasets
- The Details view allows users to "drill-down" into a data set
- Results are automatically calculated when the charting galleries are opened and re-calculated whenever outlier points are deactivated

Results Flagging and Acceptance

- ADME parameters can be flagged automatically in the Gallery (Figure 4) or in the Details view (Figure 5)
- Green, yellow or red flags indicating acceptable, questionable or rejected results, respectively, for each drug candidate
- Users can rapidly navigate to flagged data sets, and accept or reject entire data sets
- Users can filter the Gallery's viewable data sets by the flagging status to allow rapid navigation to data sets that need a scientist's manual intervention e.g., when there are outliers

FIGURE 4. Galileo LIMS Gallery View of Metabolic Stability Data with Results Flagging



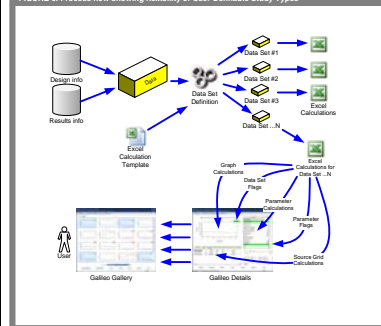
FIGURE 5. Galileo LIMS Gallery Details View of Metabolic Stability Data with Results Flagging



User-Definable Study Types & Calculations

- Microsoft Excel is used to calculate ADME parameters and prepare data for graphs
- User sees only Galileo, Excel runs in the background. Graphics are generated using Galileo, not Excel
- Multiple graphs can be created from each Details form; e.g., main plot + residuals plot + fitted plot, as specified by creator of the Excel worksheet, including horizontal and vertical bar charts
- GLP and ERES-compliant. The Excel templates, created by scientists and/or system administrators are saved inside the Oracle database, therefore, subject to system security and audit trails
- User can de-activate points in the Gallery Details form
- All of Galileo remains exactly the same. Studies designed using Design and Assays and processed using either Task Manager or RSE

FIGURE 6. Process flow showing flexibility of User-Definable Study Types



Benefits

- For ADME/Tox profiling Galileo LIMS provides simple, easy-to-use data processing, graphing, data review and reporting
- Consolidation and automation of multiple processes
- Intelligent data transfer from analytical instruments
- Elimination of manual data transfer to external software for data processing and storage (e.g., Grafit, GraphPad, SigmaPlot, or Excel®)
- Flexible calculation settings enables labs to follow their standard procedures
- Fast and easy experimental setup; no programming required
- Automatic re-calculation after outlier removal
- User-definable calculations using Microsoft Excel spreadsheets controlled and stored securely in Galileo database; adding security and allowing GLP compliance (if necessary)
- User-configurable flagging logic trees (Figure 6)
- Allows users to setup their own tree-style logic for flagging of results
- Similar to Watson's Reassay Decision Trees except that users can set up their own trees
- User-definable Accept/Reject/Flag conditions
- Color-coding based on traffic light analogy

FIGURE 7. Galileo LIMS Tree-Style Logic for Results Flagging



Conclusions

- Galileo LIMS facilitates high throughput ADME profiling and screening by providing an integrated, template-driven database system that allows rapid data review and acceptance for large numbers of compounds for metabolic stability, IC50, permeability and other in vitro ADME experiments
- The use of a system, such as Galileo LIMS, allows pharmaceutical and CRO companies to manage data efficiently and appropriately, allowing users to execute rapidly key decisions on drug candidate selection