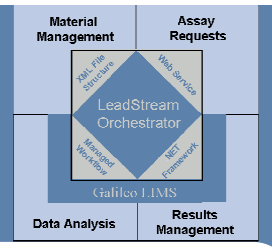
LeadStream – Galileo Integration Yields a Complete Process and Results Management Solution for ADME/Tox

Robert Dunn-Dufault, Joel Usansky, Brian Daniels, Rocky Haddad, Robert DeWitte, Marta Kozak, Andreas Stelzer, Hansjoerg Haas ● Thermo Scientific



Abstract

LeadStream™ is a fully integrated ADME/Tox screening solution, that combines role-specific automation for sample distribution and preparation, integrated LC/MS for analysis, and orchestration software for coordination of laboratory workflow. A LeadStream™ implementation is able to simplify the entire testing process from request to result, including end-to-end data tracking, automated data reduction and reporting. Recently LeadStream™ has been integrated with Galileo™, a purpose built ADME/Tox LIMS designed to enhance the manual process of data analysis, review and approval. The combined workflow of these two products provides a significant improvement in data quality, processing time, and results reporting for a range of Tier 1 and Tier 2 ADME/Tox Screens.

Introduction

The current need for preclinical ADME/Tox screening has placed demands on laboratories to deliver an increased testing throughput without sacrificing the quality of results. Quite often these two demands are in conflict. Thermo has recognized these needs by providing a scalable solution which integrates the best of breed in automation control and integration software with a purpose built LIMS system for facilitating rapid and complex data analysis.

Automated Workflow

LeadStream™ Process

The automated process depicted (Figure 1) shows the typical set of steps involved in ADME/Tox testing in the Leadstream™ Solution. A researcher submits a request for testing a set of compounds. The online application allows for the specification of a testing strategy including the set of compounds, the assays, their order, and any pass/fail criteria for subsequent assays. LeadStream Orchestrator™ uses this information to build work instructions for each of the work units and laboratory staff involved in the testing of the various assays.
Test compounds along with laboratory standards are automatically formatted on assay plates as needed (Figure 2). Information on these plates is managed by Orchestrator™ through web services. Instructions are automatically sent to the Workcell conducting the assays. Sample tracking occurs at each work unit through barcode verification. As samples are processed at a Work unit (WorkCell or LCMS) the raw data is processed in an Excel™ data reduction sheet to generate results. Results and raw data are passed back to a SQL database through webservices where Orchestrator makes automated decisions on the next testing steps. This process is cycled through each assay defined in the original request (Figure 1) . As results are generated they are automatically displayed in tabular and graphical format within the researcher web portal (Figure 3). Results are presented along with an automated QC assessment based on the results from the laboratory standards. The automated nature of this overall process makes it ideal for a high capacity tier 1 screening assays where QC processes can be fully automated. For assay requiring curve fitting, manual data review or exclusion such as in tier 2 assays a more robust analysis engine is needed such as that provided by Galileo™.

FIGURE 1. Integrated LeadStream-Galileo WorkFlow

The process begins with the submission of compounds for a defined set of assays. LeadStream Orchestrator™ handles all processing steps through to the generation of raw data and preliminary results. Through a file based link Galileo™ provides an environment for complex analysis, curve fitting and manual Quality Control.

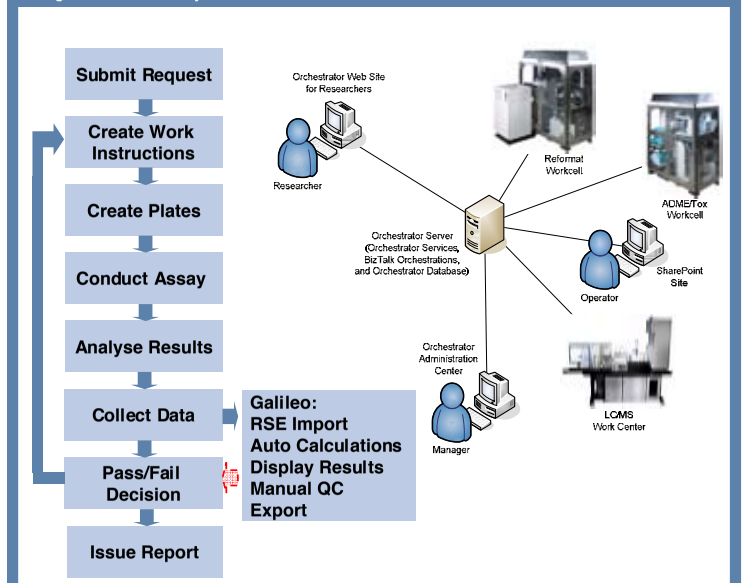


FIGURE 2. Orchestrated Sample Management from Preparation to Results

All automated instrumentation and human tasks are managed by LeadStream Orchestrator™. Samples are automatically created and processed through the various work units according to the requirements of the ADME/Tox assays in the test plan. All assay results and raw data are automatically passed back to the Orchestrator for storage and presentation.

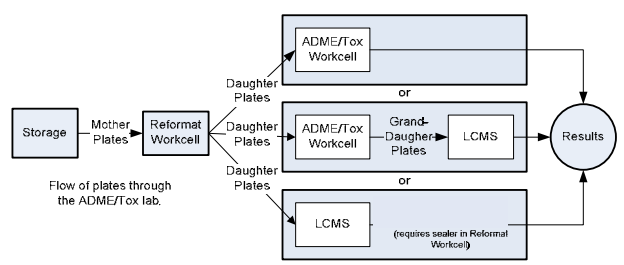


FIGURE 3. Automatic Web based reporting

Researchers receive e-mail notification when testing is complete and can also access web-based reports. Data is automatically populated as soon as it is available.

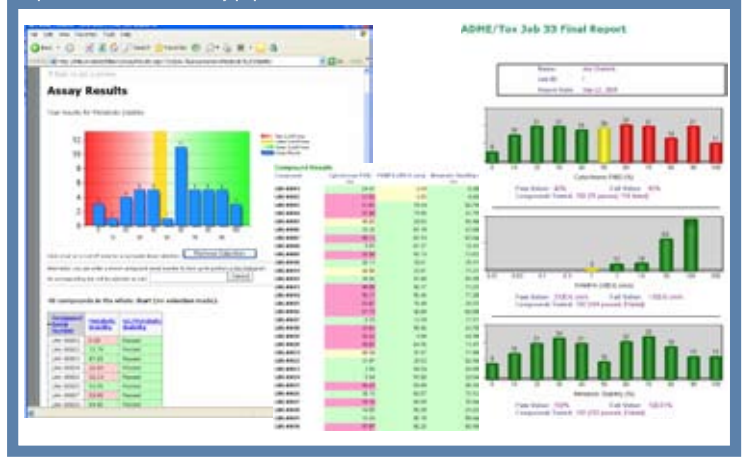


FIGURE 4. Result Import, Graphing and Review in Galileo™.

Raw data and results created in LeadStream are pulled from the database and automatically formatted for entry into Galileo™ through a Rapid Study Entry Process.

Once Data has been brought in to Galileo™ it is processed according to the assay protocol and presented graphically for detailed QC review.

Galileo™ Integration

Galileo™ was designed for rapid implementation with minimal configuration. It supports a wide range of screening and ADME assays such as permeability, metabolic stability, IC50, Ki, enzyme kinetics, protein binding and mechanism based inactivation.
Raw data and results created in LeadStream™ are pulled from the database and automatically formatted for entry into Galileo™ through a Rapid Study Entry Process (Figure 4). Once data has been brought in to Galileo™ it is processed according to the assay protocol and presented graphical for detailed QC review.
Galileo™ is a fully integrated LIMS that allows users to design, automatically calculate and graph in vitro ADME/Tox experiments in a single application. Graphical multi-plot galleries allow the user to rapidly review and accept data. Simultaneous fitting of data to multiple models allow numerical and graphical comparison when assessing results. The complete set of raw data, calculated results and user annotation are stored in a secure database for archiving or export.

Summary

The current level of integration of LeadStream with Galileo™ provides several benefits to the ADME/Tox screening process:

- Highly automated testing matching custom test plans
- Dynamic closed loop workflows
- Tightly integrated data and process tracking
- Rapid data review, results flagging, and acceptance
- Versatile non-linear fitting algorithms
- Powerful viewing and reporting
- automatic data storage

Future Work

Work will continue on the integration of these two products in two ways:

1. Bidirectional communication

Galileo™ QC results will be passed back to LeadStream™ through webservices. LeadStream™ will take the flagged data and depending on the flagged status of each Compound will make decisions on next steps in the workflow or for retesting in the current assay.

2. Real-time fully automated QC evaluation in Galileo™

When laboratories are satisfied that they have defined a robust QC criteria in Galileo™ the system would be activated for walk away mode. Only compounds flagged as requiring human evaluation will be reviewed in an offline process.

Thermo SCIENTIFIC