

Achieving Ultra High Performance Screening

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Abstract

High throughput (HT) and Ultra High Throughput (UHT) screening remains a valuable and necessary approach to modern drug discovery. With the use of numerous standardized biochemical assays now commonplace, successful application of HTS requires accurate and meaningful handling of the experimental results. Specifically, this means capturing vast data volumes generated by HTS and UHTS programmes and subsequent validation and verification. Decision making regarding HTS data can be supported via comprehensive and intuitive visualization of results. Also important is the establishment and maintenance of analysis templates for this type of experiment. In order for HTS and UHTS to be successfully implemented in drug discovery, all the aforementioned issues must be addressed.

Introduction

High throughput screening strategies are now commonly used in drug discovery to identify compounds with desirable chemical properties or behaviors. These campaigns are characterized by performing single or, sometimes, multiple assays on large numbers of chemical compounds, resulting in the production of large data volumes. It is the handling and manipulation of this data, that poses a significant challenge to scientists today. The following areas are highlighted as being fundamental regarding HTS data management :

- Provision of a single test environment to encourage straightforward workflow and reduce possibility of error being introduced between applications
- Robust, flexible and user definable validation criteria for captured data
- Minimize resource for the design and maintenance of analysis templates
- Ensure access to all anticipated statistical analysis tools
- Impose full user control over what data is published to central repositories

Building on successful implementation in over 200 pharmaceutical companies worldwide, IDBS sought an improved data management solution for high throughput screening. Focusing on improved workflow, data validation, verification and visualization, and template design and maintenance, ActivityBase Xtended Edition was introduced.

Methods

Improved Workflow

ActivityBase XE provides one environment in which all required data manipulations and visualizations can be performed. In addition to the obvious time saving achieved by using one single environment, the potential for transcription errors is reduced. For a medium-sized installation, assume 50 users, and on average 15 minutes per user is saved per day. For an average working year of 220 days. This equates to approximately 73 recovered man weeks/year through improved workflow.

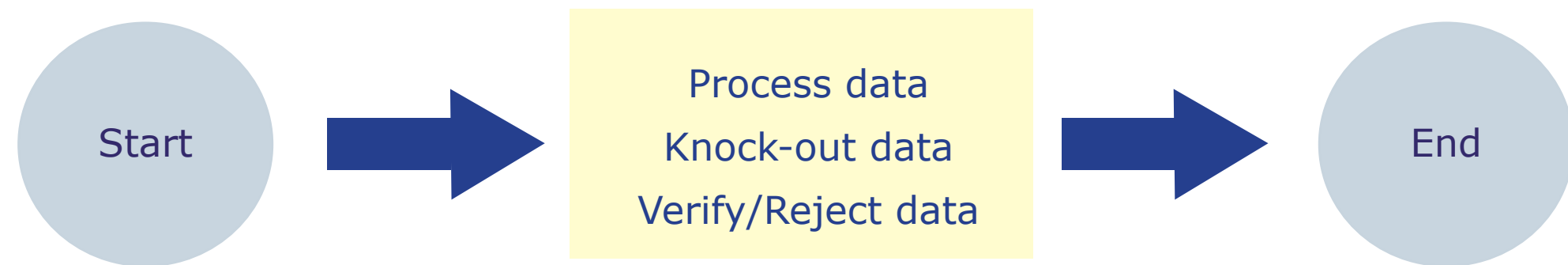


Figure 1. Example workflow using ActivityBase XE

User Definable Data Validation

High data volumes necessitate comprehensive, yet flexible, data quality assurance options. Outlier results are brought to the user's attention through graphical representation or can be automatically excluded from subsequent analysis. This can be done at either the plate or well level. Such data validation ensures that only representative data is published to the central database - which ultimately supports better decision making.

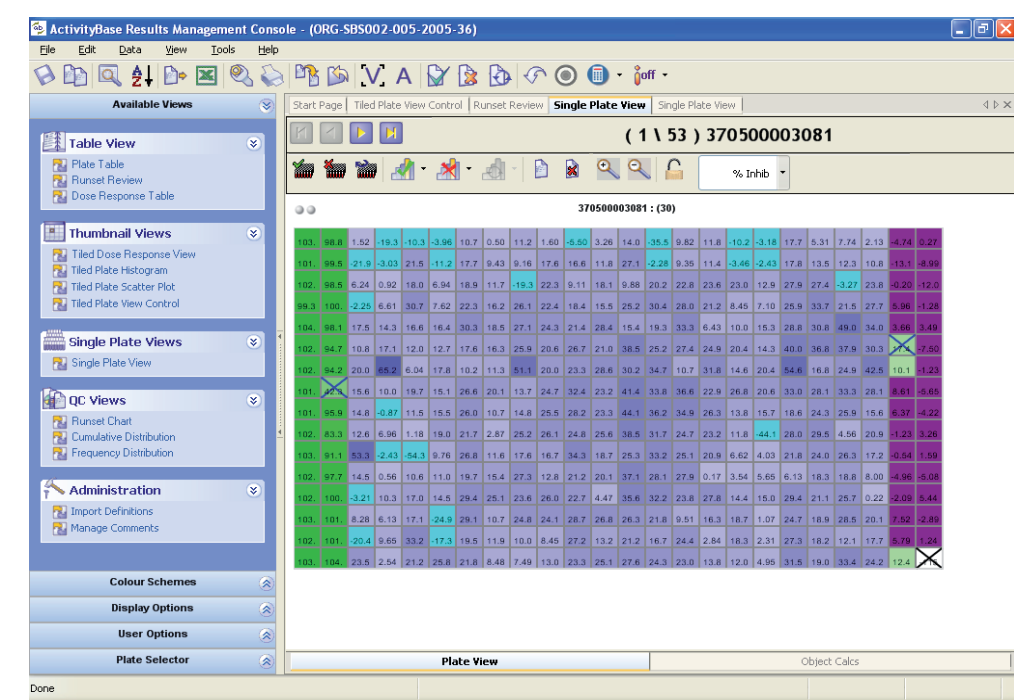


Figure 2. Control well results outside pre-defined limits have been automatically excluded

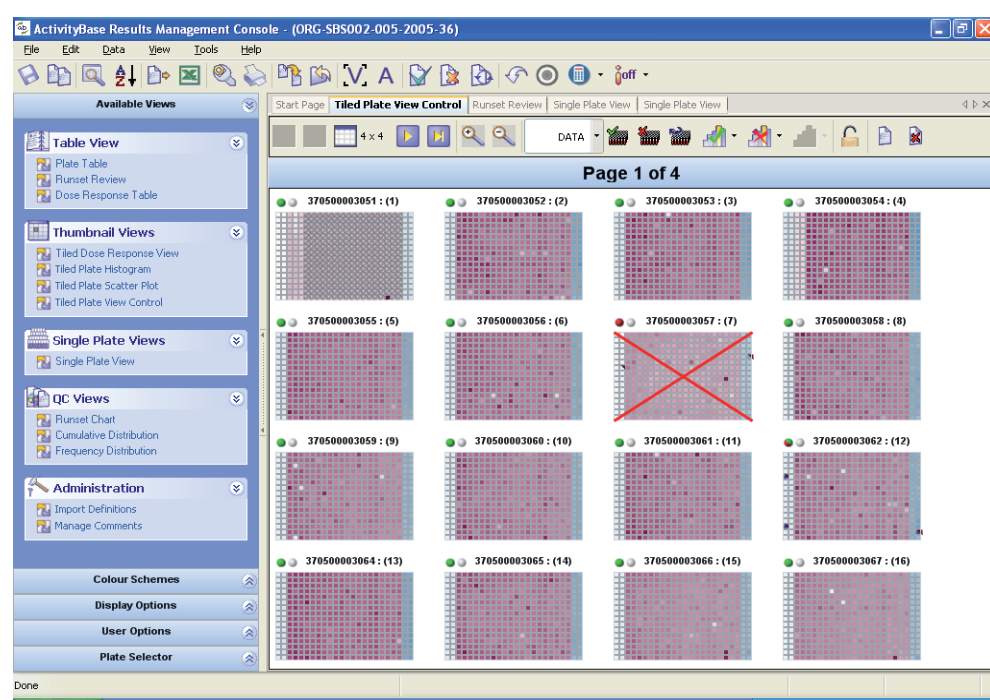


Figure 3. Following automatic data acquisition from a plate reader, Z-prime results outside predefined limits lead to the exclusion of the whole plate from future analysis

Analysis Template Design

ActivityBase XE contains design and publishing capabilities for the development of analysis templates. The XE Designer is an excellent complement to standard spreadsheet packages, providing:

- The ability to construct formulae once and apply them throughout an analysis template. This eliminates the risks associated with copying the same formula many times across a spreadsheet
- The ability to reuse templates through the Master Template facility. This means that most templates can be constructed as variations on an existing template design, drastically reducing the time taken to create new templates
- Features that enable the user to react to changes in a Protocol by changing elements of an existing template without extensive rebuilding. This dramatically reduces the burden of maintaining templates in a changing environment
- The ability to change plate formats within a template without rebuilding related calculations. This reduces the time taken to work with new plate formats
- Error checking prior to publishing of analysis templates

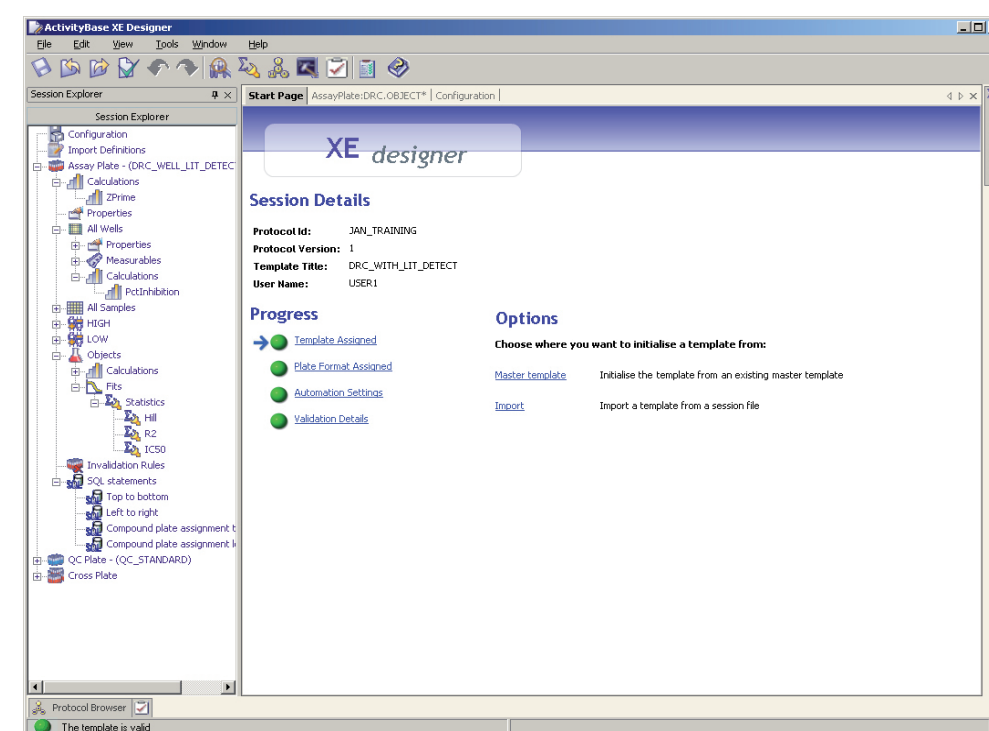


Figure 4. Assisted workflow for template creation

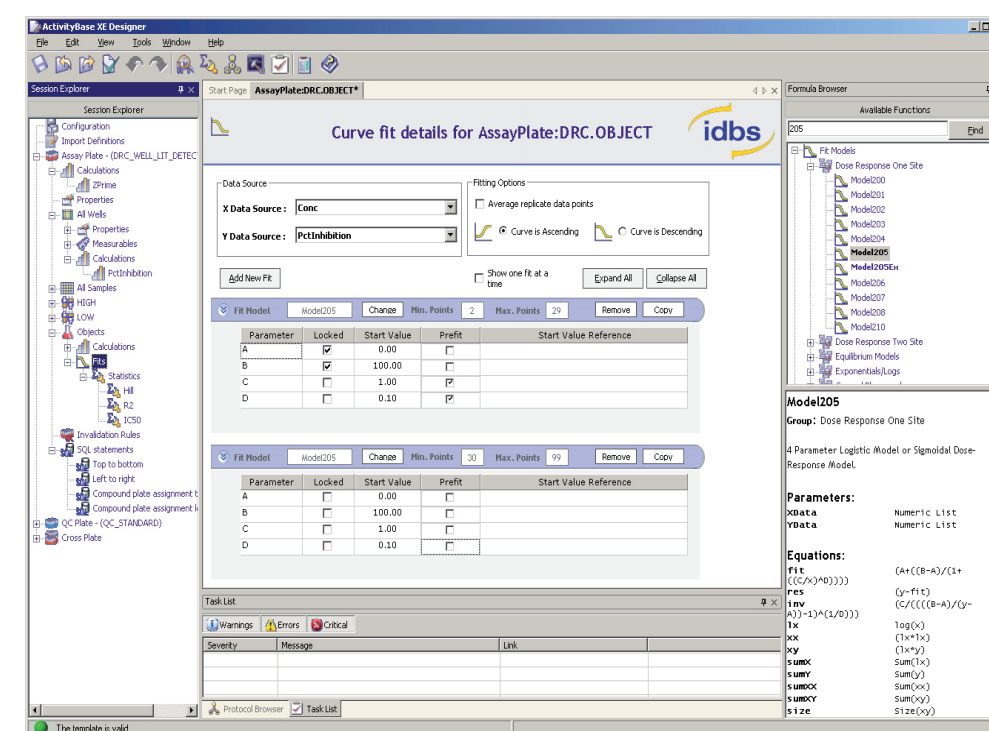


Figure 5. Flexible intuitive curve fitting within XE Designer

Statistical Analysis Options

The internal statistic engine provides all the required functionality regarding analysis and curve fitting of results. Data can be presented as 2D graphs. Users also have the opportunity to enter their own statistical analysis into this engine.

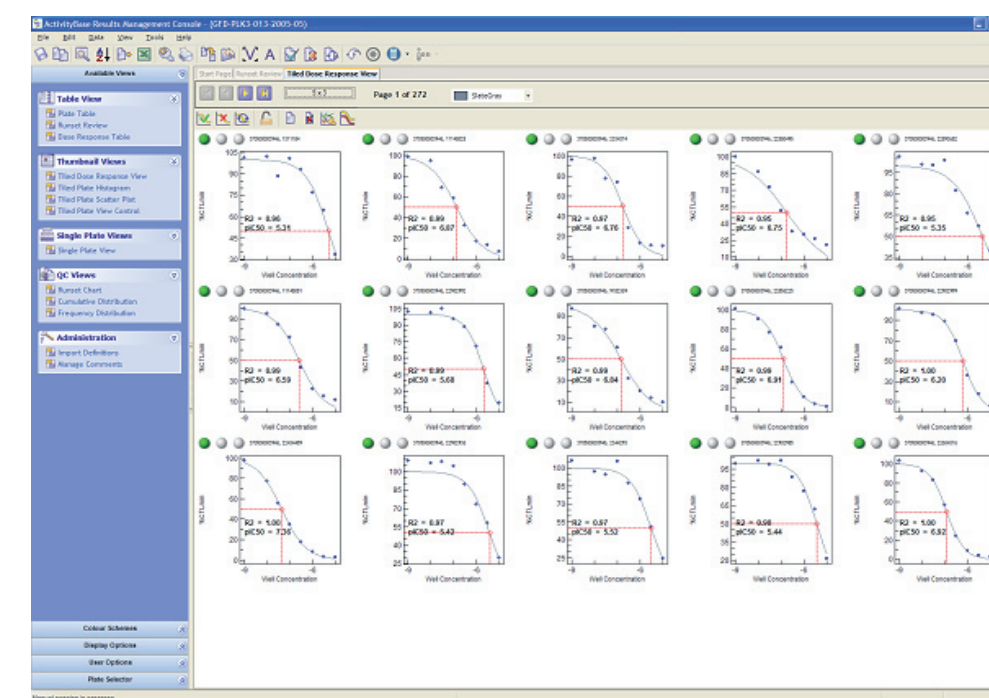


Figure 6. Tile view of dose response curves showing current QA status

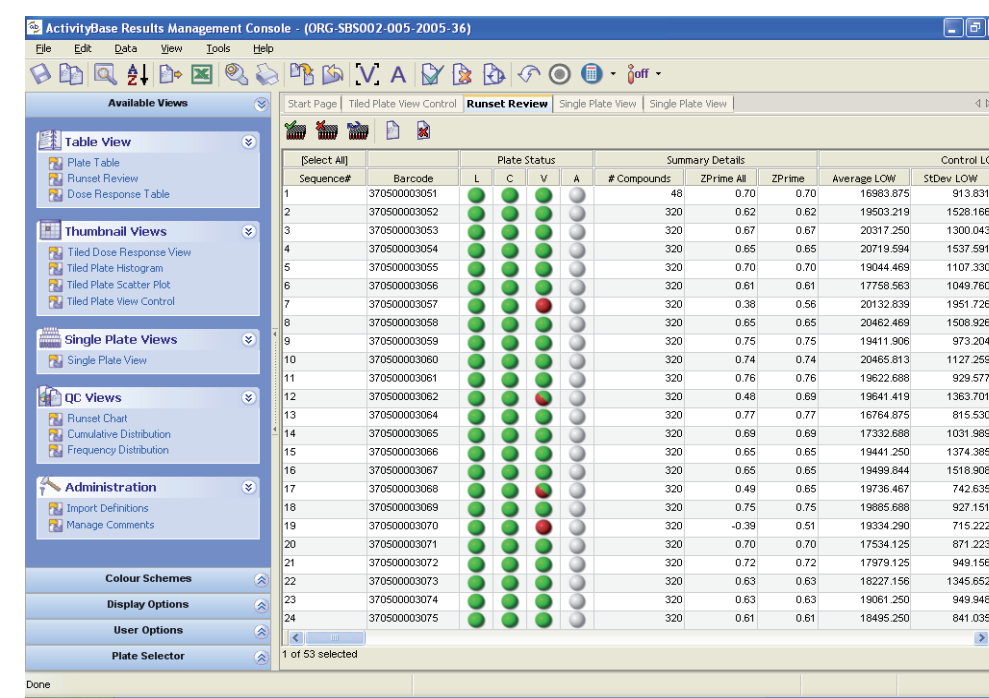


Figure 7. Testset view detailing summary data and statistical summary

Results verification

Prior to publishing to the underlying ActivityBase database, results are viewed and verified as correct. A list displays all plates, together with the validation status and summary statistical information regarding the plate (e.g. Z-Prime and number of compounds on plate).

Conclusion

ActivityBase XE has been designed to accommodate the workflow requirements of HTS and UHTS experiments. Experimental data management, including storage and analysis, in one environment provides significant improvement in workflow. Reduced reliance on external spreadsheet packages for template design and publishing together with in-built error checking significantly reduces the maintenance burden. The combination of both automatic and interactive validation and verification options ensure timely and accurate analysis of results.

In summary, ActivityBase XE provides:

- Improved screening efficiency through improved experimental workflow
- A complete package for HTS data handling, including automated data capture, flexible data display and a robust supporting data management system
- Both automatic and interactive validation/verification of results
- Significant return on investment through an improved data handling process and efficient template design and maintenance
- Provides one integrated solution to all HTS and UHTS requirements