Enhanced Incurred Sample Reanalysis (ISR) in Watson LIMS

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Introduction

During drug development programs, bioanalytical assays are validated and used to quantify drugs and their metabolites in samples from a variety of different biological matrices. Incurred Sample Reanalysis (ISR) has recently become an accepted way to assess the quality of bioanalytical assays and is widely used within the pharmaceutical industry and by contract research organizations for this purpose. ISR occurs when samples obtained from an in-vivo study are re-analyzed to demonstrate that the assay is reproducible.

The concept of incurred sample reanalysis was established in the third AAPS/FDA bioanalytical workshop/conference report[1] where it was stated that performance of spiked standards and QCs may not adequately mimic that of study samples from dosed subjects, that is, incurred samples.

A follow-up workshop was convened to provide a forum for consensus building about incurred sample reproducibility for both large and small molecules. The June 2009 report[2] provides recommendations for ISR assessment, studies that should be tested, the selection of samples, and acceptance criteria. Some highlights are:

• Individual samples, not pooled samples, should be used for ISR testing
• ISR analysis should be conducted on the same number of replicates (singlet, duplicate, etc.) as the original analysis
• The number of samples repeated for ISR analysis should be 5-10% of the total sample size, and 5% for larger studies
• Selecting fewer samples from more subjects is better than full PK profiles
• Analyze samples near the T_{max} and near the end of the elimination phase
• Acceptance criteria for small molecules (non-ligand binding assays) is 2/3 of the repeat samples should agree within 20%, and for ligand-binding assays 2/3 of the repeat samples should agree within 30%
• Results from or reference to ISR assessments should be included in the report of the study from which samples were taken.

The most recent paper by Timmerman et al.[3] published in October 2009, representing the European Bioanalysis Forum, presents an alternate viewpoint on selected aspects of ISR. It points out changes in the evolution of ISR philosophy over time, and introduced a new concept that failed ISR may be due to either poor assay methodology or poor bioanalytical execution, and made recommendations for the frequency of ISR bioanalysis and selection of studies.

ISR in Watson 7.4

Thermo Scientific Watson LIMS is the most commonly used bioanalytical data system in the pharmaceutical industry. Watson™ allows users to conduct incurred sample reanalysis and reporting. Recently, enhancements have been introduced into Watson that afford bioanalysts greater control in the way that ISR samples are added to a Watson worklist. In addition, reporting features have been substantially improved yielding more functionality and greater ease-of-use.

• Ability to have ISR samples within same run as regular bioanalytical samples
• Separate Mandatory Repeats run is no longer required
• Mandatory Repeats run type has been discontinued
• New sample type called "Incurred Sample Repeat" type (analogous to Reassay tagging)
• Ability to have the Stds, QCs, and curve parameters from runs with ISR samples included in the Assay Precision reports

ISR in Watson 7.4.1

New features of ISR in Watson 7.4.1 are:

• Ability to run Immune Response Module (IRM) samples as ISR samples
• Ability to report on Concentration, IRM or both types of samples
• Ability to pre-define the default reporting template to be used
• Ability to report on Mandatory Repeats runs, ISR samples, or both

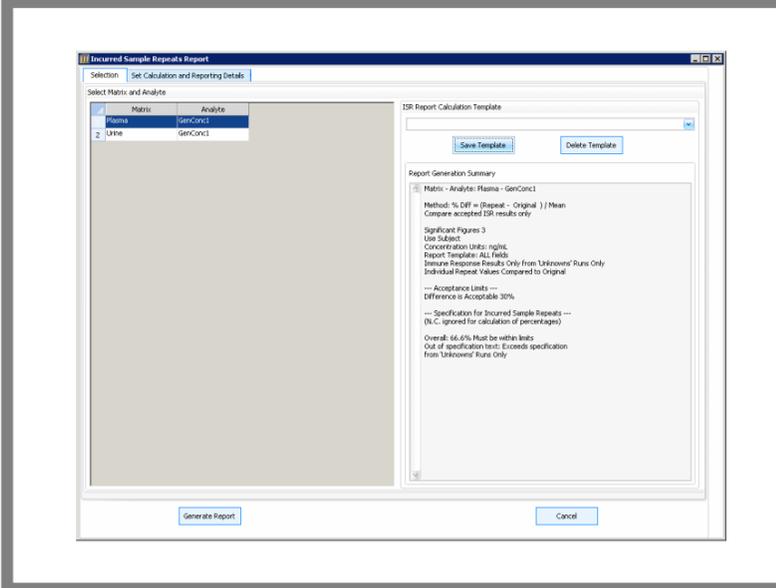FIGURE 1. ISR report setup form showing the selection of calculation templates

FIGURE 2. ISR report setup form showing the definition of calculations for the incurred samples. Red boxes highlight enhancements added to Watson 7.4.1
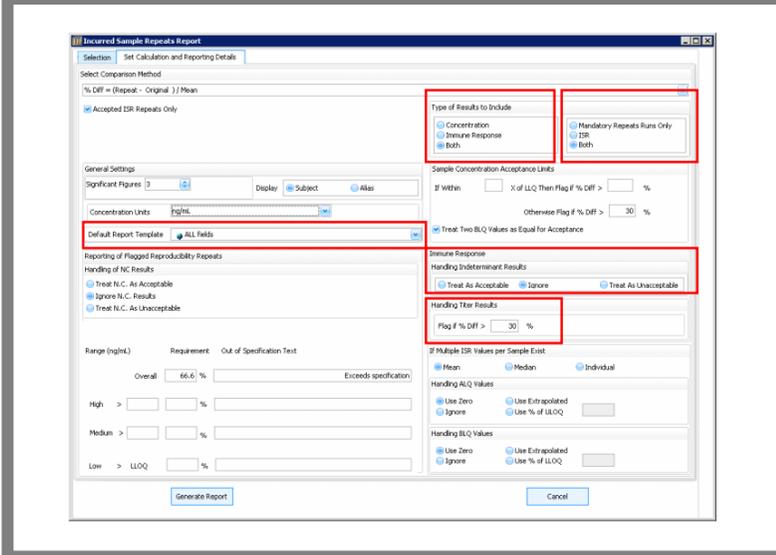

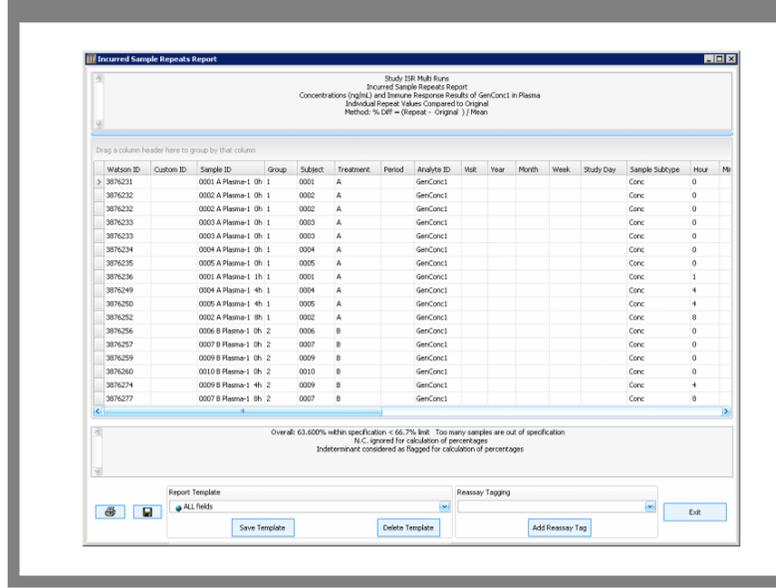FIGURE 3. Typical incurred sample reanalysis (ISR) report from Watson LIMS

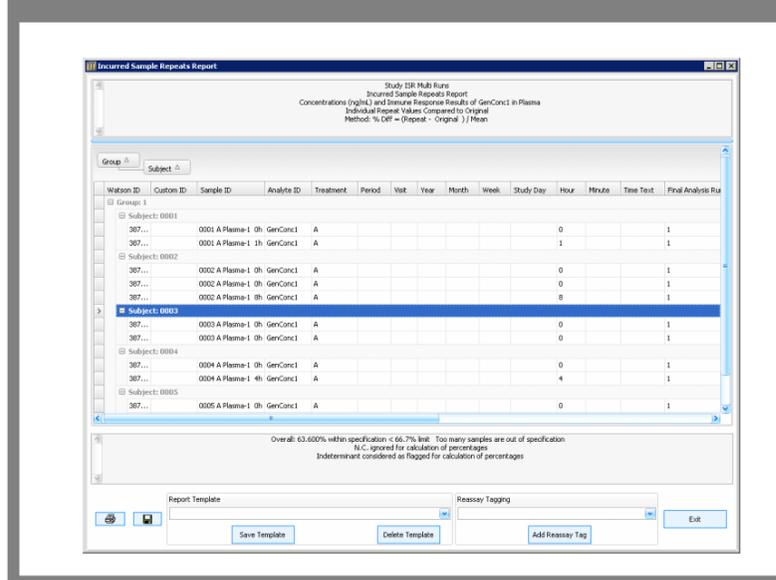FIGURE 4. Incurred sample reanalysis report which has been grouped by Group then Subject

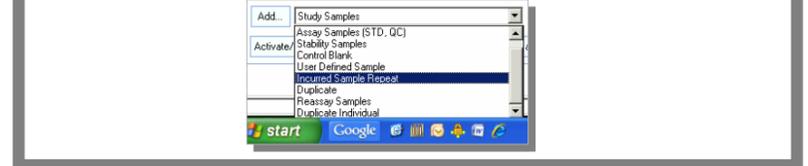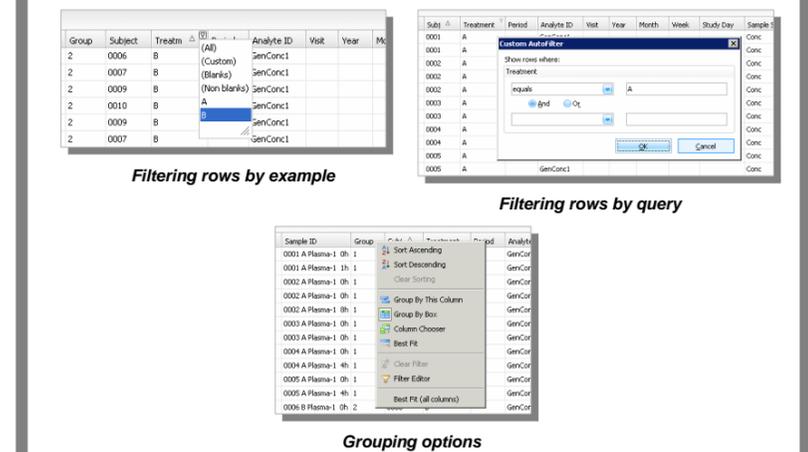FIGURE 5. Adding ISR Samples to an analytical run

FIGURE 6. The user can filter and group rows in the ISR report using techniques similar to spreadsheet applications

Filtering rows by example

Filtering rows by query

Grouping options

Conclusions

The Incurred Sample Reanalysis features of Watson have been extended to allow for reporting of Immune Response Module data and other reporting enhancements. Processing and reporting of ISR data by Watson has been made faster and even more flexible.

References

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3. P. Timmerman, S. Luedtke, P. van Amsterdam, M. Brudny-Kloeppel and B. Lausecker. Incurred sample reproducibility: views and recommendations from the European Bioanalytical Forum. Bioanalysis 1(6), 1049-1056, 2009