

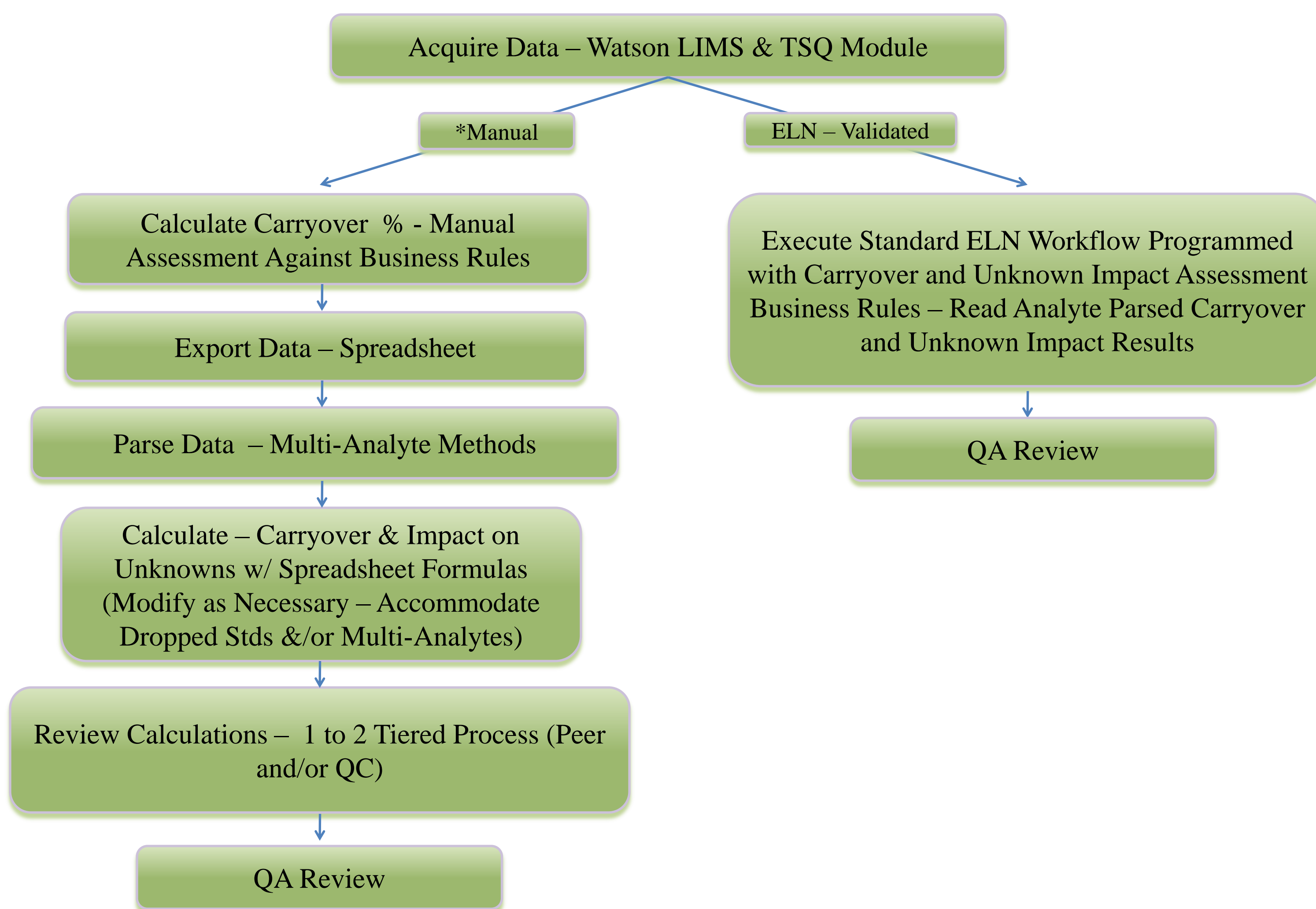
Objective

Methods for evaluating the impact of carryover on unknown samples in regulated bioanalytical studies vary greatly. Furthermore, the handling of data sets with carryover exceeding procedural tolerances is equally variable. Where data may be accepted after impact assessment, the process often involves exporting data to perform calculations in spreadsheets. Although the math is quite simple, the calculations, and more so, the review of these calculations, in a regulated laboratory can be time consuming without a validated, automated process in place. The model presented here illustrates an automated carryover acceptance and impact evaluation scheme. It is performed via a validated electronic laboratory notebook (ELN) workflow which polls Watson LIMS for appropriate raw data on a run-by-run basis. The user is presented with a list of all impacted samples requiring reassay within the customized ELN (IDBS E-WorkBook Suite).

Methods

Workflows representing i.) an example of a traditional carryover impact assessment scheme, and ii.) an automated, validated approach are presented in the figure below.

Expansion of the automated ELN workflow from ii.) above is presented in subsequent figures.

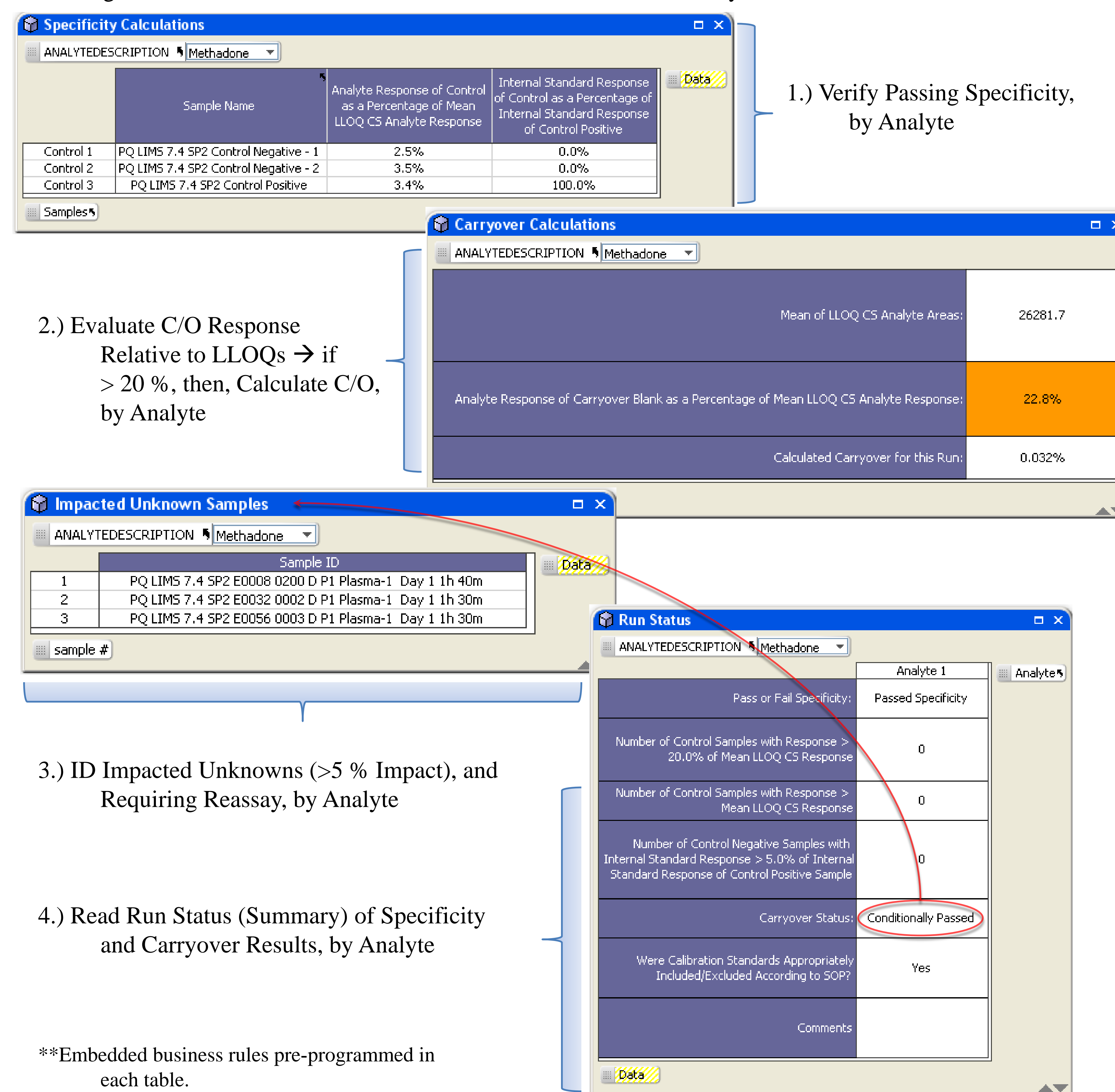


*Manual workflows to assess carryover acceptance and to evaluate impact on unknowns depend upon business rules and systems in place. In this example scheme, the model assumes i.) a multi-analyte method, ii.) carryover acceptance based on carryover blank response as a %-age of a mean, LLOQ Std response, iii.) unknown impact assessment based on carryover %-age calculated, and iv.) use of Watson LIMS.

Methods (Cont.)

Data is acquired directly into Watson LIMS via the TSQ Module interface for a Thermo Vantage mass spectrometer. The validated ELN workflow calculates the response of the carryover blank sample relative to the mean of the two lowest calibration standards in the run. Carryover (C/O) blank response greater than 20.0 % of this mean initiates an automated impact assessment on unknown samples. Percent carryover is determined by dividing the carryover blank area by the calibrator area immediately preceding it. Impact is evaluated by calculating the percent increase in sample response expected from the prior injection. Samples with a percent increase in response from the prior injection greater than 5 % are reported in a sorted sample list as flagged for reassay.

**In figures below, the ELN workflow is executed once for a dual-analyte, methadone and EDDP run:



1.) Verify Passing Specificity, by Analyte

Sample Name	Analyte Response of Control as a Percentage of Mean LLOQ CS Analyte Response	Internal Standard Response of Control as a Percentage of Internal Standard Response of Control Positive	
Control 1	PQ LIMS 7.4 SP2 Control Negative - 1	2.5%	0.0%
Control 2	PQ LIMS 7.4 SP2 Control Negative - 2	3.5%	0.0%
Control 3	PQ LIMS 7.4 SP2 Control Positive	3.4%	100.0%

2.) Evaluate C/O Response Relative to LLOQs → if > 20 %, then, Calculate C/O, by Analyte

Mean of LLOQ CS Analyte Areas:	26281.7
Analyte Response of Carryover Blank as a Percentage of Mean LLOQ CS Analyte Response:	22.8%
Calculated Carryover for this Run:	0.032%

3.) ID Impacted Unknowns (>5 % Impact), and Requiring Reassay, by Analyte

Sample ID	Sample Name
1	PQ LIMS 7.4 SP2 E0008 0200 D P1 Plasma-1 Day 1 1h 40m
2	PQ LIMS 7.4 SP2 E0032 0002 D P1 Plasma-1 Day 1 1h 30m
3	PQ LIMS 7.4 SP2 E0056 0003 D P1 Plasma-1 Day 1 1h 30m

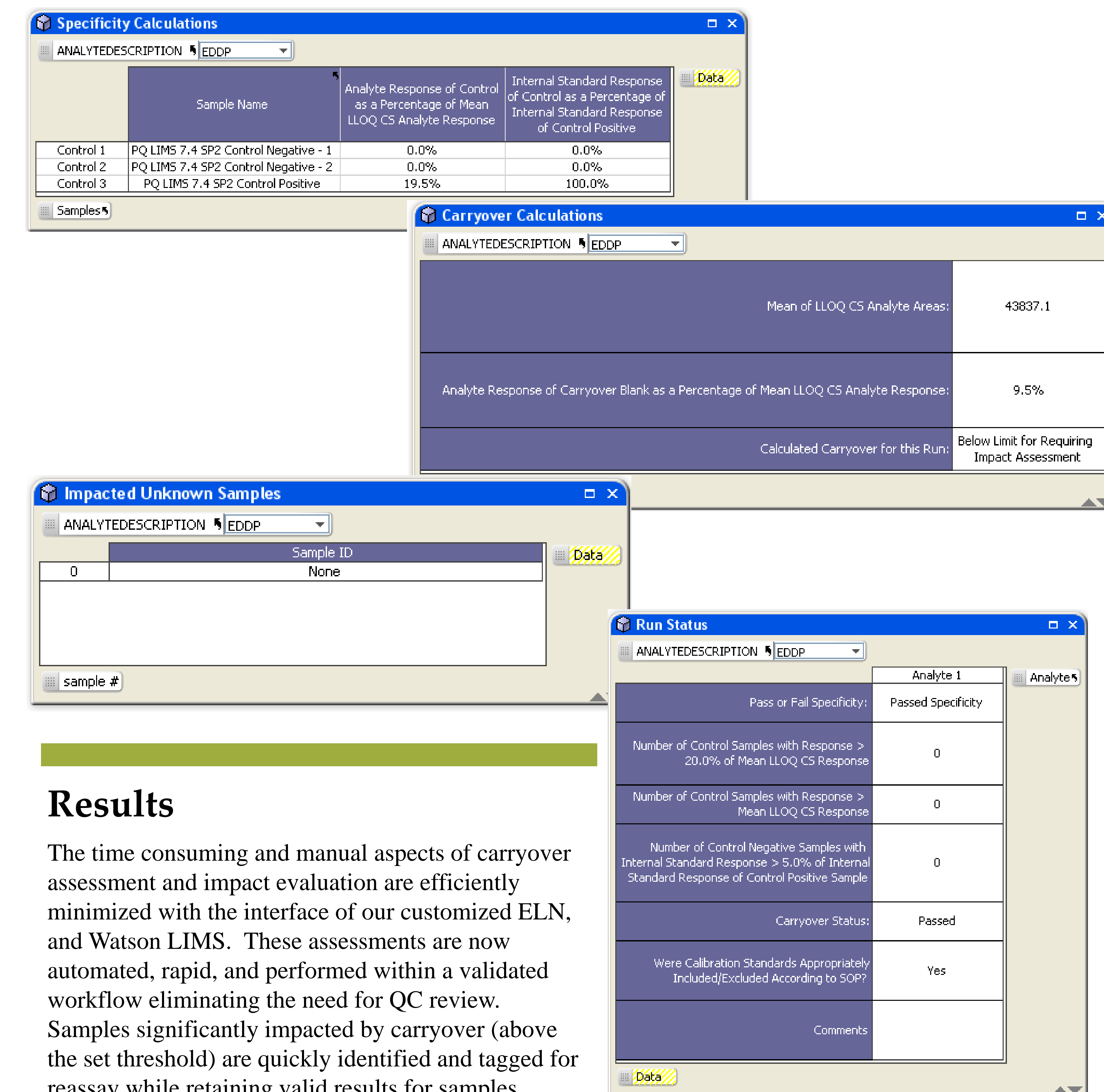
4.) Read Run Status (Summary) of Specificity and Carryover Results, by Analyte

Pass or Fail Specificity:	Analyte 1
Number of Control Samples with Response > 20.0% of Mean LLOQ CS Response	0
Number of Control Samples with Response > Mean LLOQ CS Response	0
Number of Control Negative Samples with Internal Standard Response > 5.0% of Internal Standard Response of Control Positive Sample	0
Carryover Status:	Conditionally Passed
Were Calibration Standards Appropriately Included/Excluded According to SOP?	Yes
Comments	

**Embedded business rules pre-programmed in each table.

Methods (Cont.)

Independent run results for the second analyte (EDDP) reported in the same executed workflow instance :



Mean of LLOQ CS Analyte Areas: 43837.1

Analyte Response of Carryover Blank as a Percentage of Mean LLOQ CS Analyte Response: 9.5%

Calculated Carryover for this Run: Below Limit for Requiring Impact Assessment

Sample ID: None

Pass or Fail Specificity:	Analyte 1
Number of Control Samples with Response > 20.0% of Mean LLOQ CS Response	0
Number of Control Samples with Response > Mean LLOQ CS Response	0
Number of Control Negative Samples with Internal Standard Response > 5.0% of Internal Standard Response of Control Positive Sample	0
Carryover Status:	Passed
Were Calibration Standards Appropriately Included/Excluded According to SOP?	Yes
Comments	

Results

The time consuming and manual aspects of carryover assessment and impact evaluation are efficiently minimized with the interface of our customized ELN, and Watson LIMS. These assessments are now automated, rapid, and performed within a validated workflow eliminating the need for QC review. Samples significantly impacted by carryover (above the set threshold) are quickly identified and tagged for reassay while retaining valid results for samples insignificantly impacted.

Conclusions

Integration of a custom, validated ELN workflow with Watson LIMS eliminates time-consuming manual processes for determining carryover acceptance and impact. This also eliminates the need for QC review of these tasks, further increasing efficiency.