

Method Validation Report Generation Using Word97 Automation

John W. Cornacchia, Scott Serl, Jeri M. Willoh, Mike H. Buonarotti and Robert A. Bethem *Alta Analytical Laboratory, El Dorado Hills, CA 95762*
Ike D. Tabani, Mikhail Amchislavsky and Gary Peterson *Innovative Automation, Sacramento, CA 95823*

Introduction

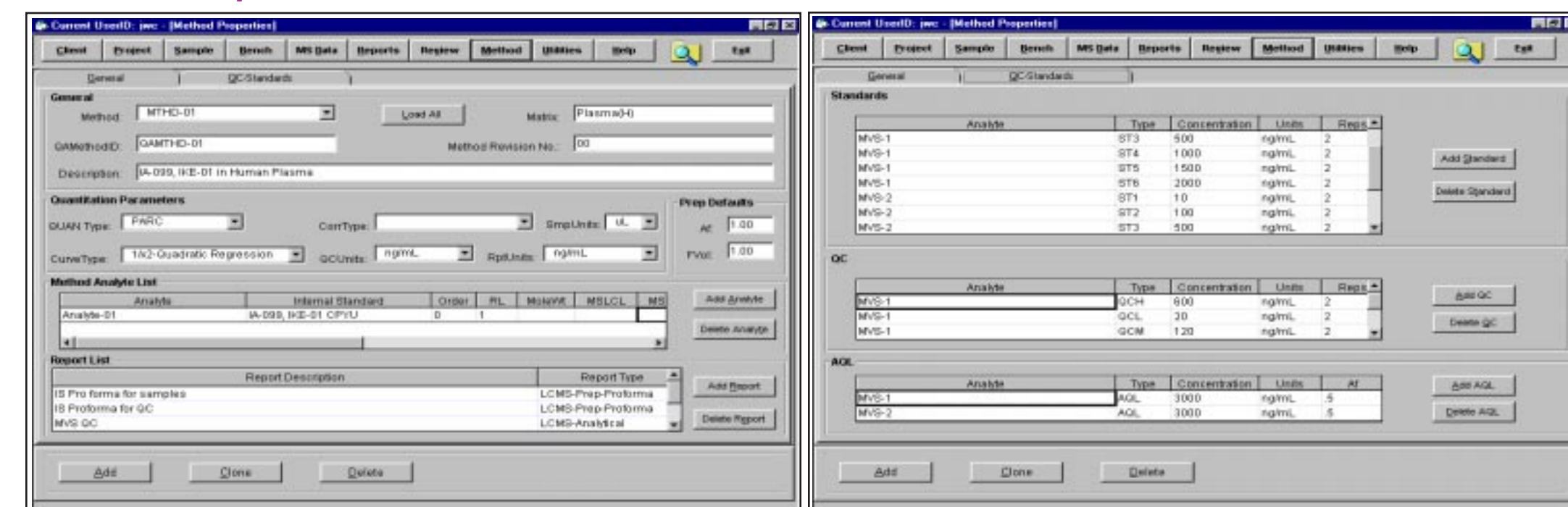
Bioanalytical method validation studies require processing of method performance data and generation of custom analytical reports. Although there is some similarity between LCMS method validation plans, CRO's typically are required to use experimental designs and report table templates that vary due to compound or sponsor driven requirements. These factors complicate any efforts to standardize and streamline report generation via software automation.

In this poster, we describe our approach using ALIS98, an LCMS Reportwriter, and MS Word97. ALIS98 provides a method validation set-up wizard, method templates, electronic benchsheets and computational modules needed to set-up and process method validation data. ALIS98 results are stored in MS Access97 and are queried into formatted Word templates using SQL. This approach has enabled rapid automated production of report tables and has reduced transcriptional errors and inconsistent numerical formatting.

1 Method Setup

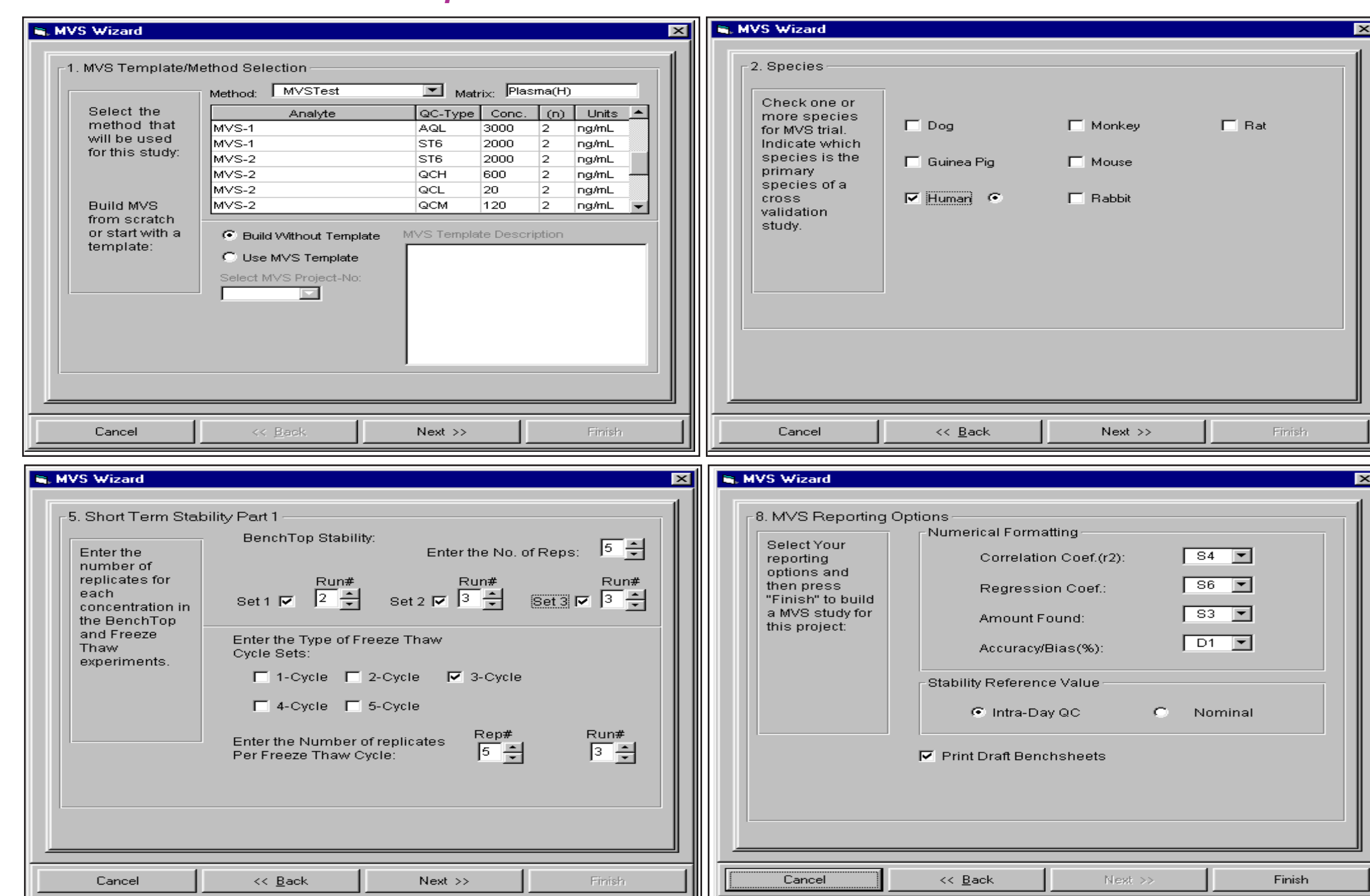
In the first step, a method template is created in Alis98 that includes the analyte list, reporting limits, method specific report forms, computational parameters (including regression curve fitting model) and the instrument response type (screen, lower left).

Method Setup General Information



The concentration levels and number of replicates that define the calibration curve and QC sets are also entered into the method template. This set-up information is used by the MVS Set-up wizard (below) to generate laboratory benchsheets that match both the method dynamic range as well as the MVS experimental design.

Method Validation Plan Set-up Wizard

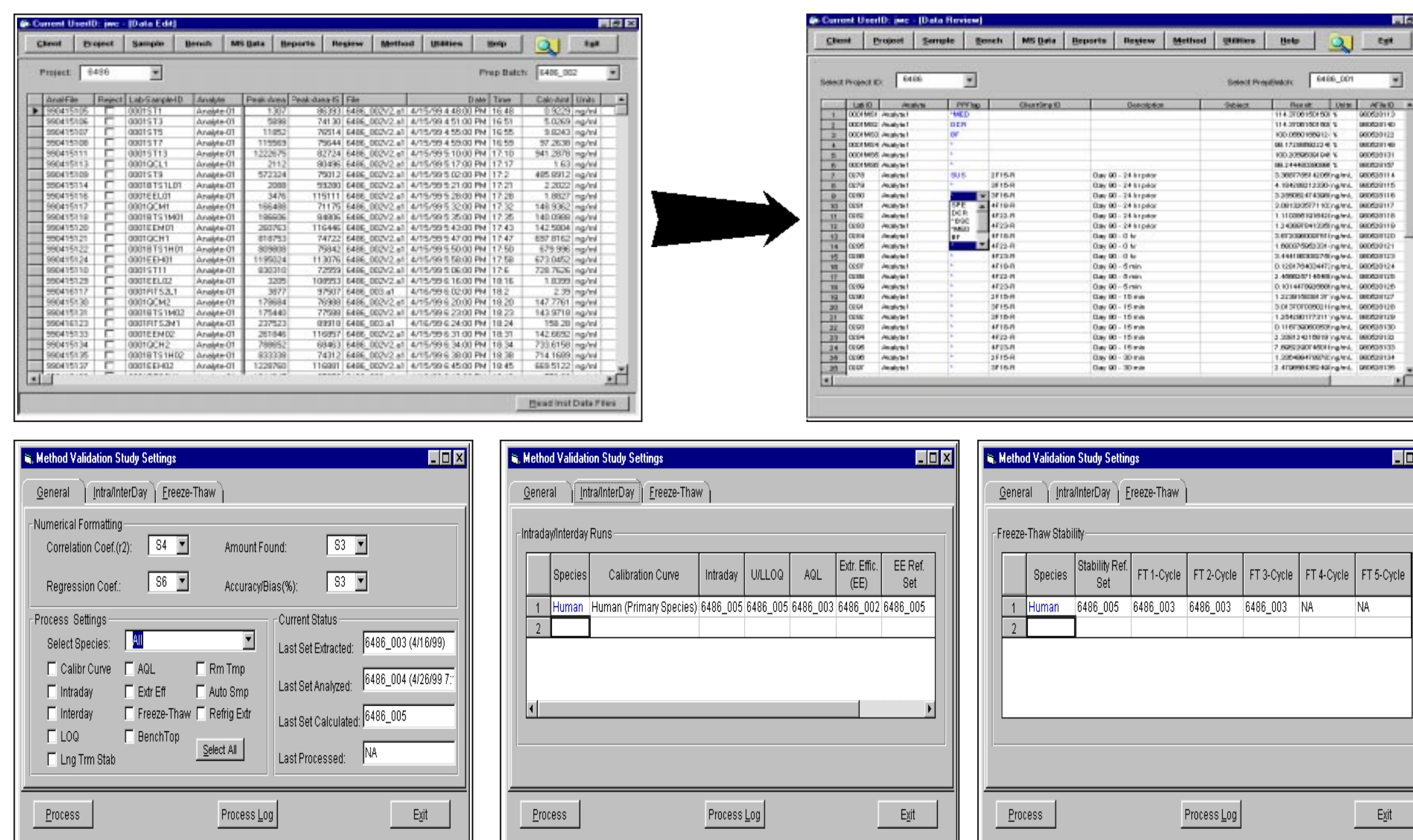
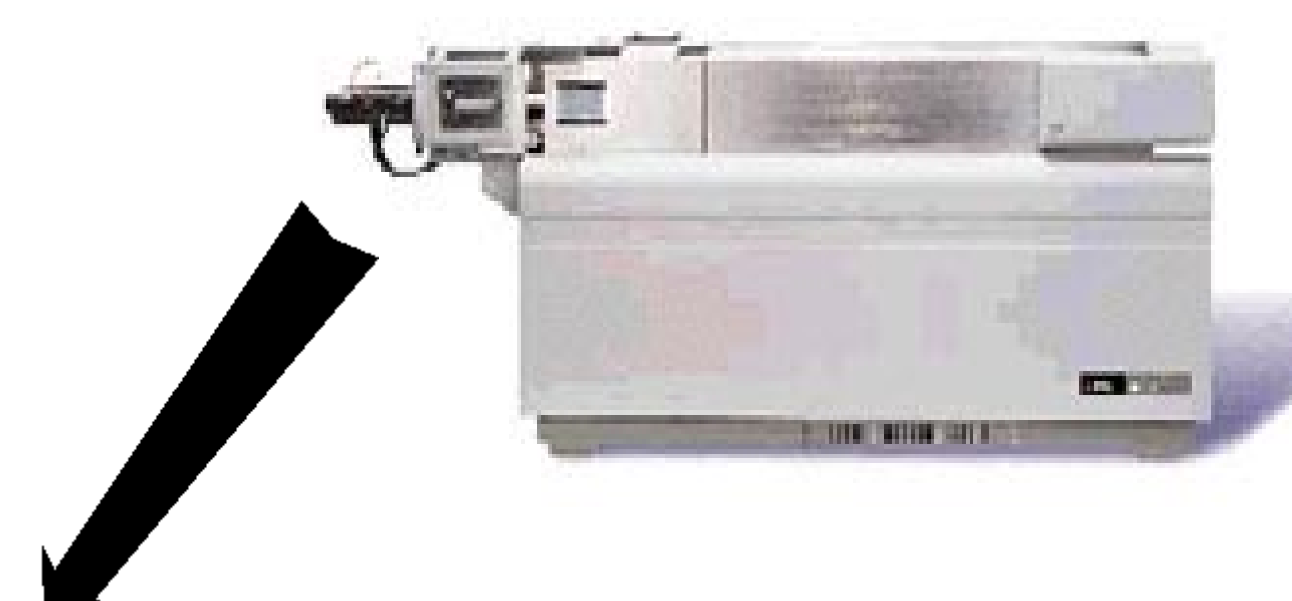


In the next step, the MVS plan is entered into ALIS98 utilizing a MVS wizard (example screens are shown above). The wizard prompts the user to enter the number of replicates for each validation trial including AQL, LOQ, intra/inter variability studies and stability trials (benchtop, freeze-thaw, refrigerated extract, auto-sampler stability). Each stability trial may include multiple time intervals. Report numerical formatting (decimal or significant figure formats) can be assigned during set-up.

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LC/MS Instrument Data File Upload, Analytical Data Review & Method Validation Database Production

Following sample analysis, LCMS/MS instrument text output files from PE/Sciex API III/365/3000 data systems can be uploaded interactively or in a batch mode. Uploaded files are parsed and stored into ALIS98 database tables. Instrument data files can then be viewed and flagged prior to final result calculation (screen lower left). The calculation subroutines screen results and automatically flag any values outside the calibration range or other user defined criteria (screen lower right). Analytical reports are generated using Crystal Reports 6 incorporating custom templates and significant figure libraries. The report output may be exported in a variety of file formats and routed for group distribution via email or hard copy reports.



After reviewing analytical results, the user may select a set to be used for the "zero-day" recovery calculation. In addition, numerical formatting (e.g. significant figure rule) may be defined for each reporting parameter including correlation and regression coefficients, amount found, per cent accuracy and bias. Method validation data may be reprocessed by experiment, i.e., in part or all. All results are exported into a separate Access97 database file (MDB) and may be queried into Word97 utilizing the MS DAO 3.5 library.

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Word-97 VBA Automation & Customized Report Production

In the final step, a custom Visual Basic for Applications (VBA) program is utilized to extract processed method validation results data from ALIS98 stored in Access97 database tables. The module then populates pre-defined Word-97 report templates using the extracted data. The user interface containing all method validation report components is displayed (screen lower left) and the user can interactively select one or all tables. MVS report tables are automatically numbered, paginated and stored in a designated project directory. Supported report tables currently include calibration summaries, intra/interday QC, ULOQ/LLOQ, AQL, benchtop stability, freeze/thaw stability, autosampler stability, refrigerated extract stability and long term stock solution stability (see examples below).

Word-97 VBA Module

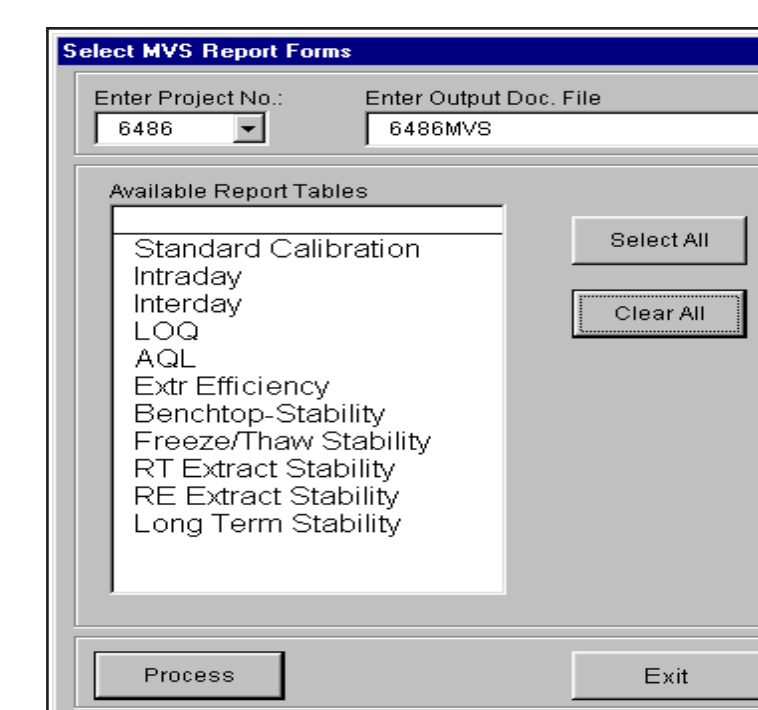


Table 1. Calibration Curve Data (Human Plasma(H)).

Run #	Standard Concentrations of Analyte-01											
	1	5	10	50	100	500	750	1000	Accuracy	Accuracy		
6486_002	0.943	94.3	4.34	98.8	9.61	96.1	95.2	51.5	103	738	96.5	96.7
6486_003	0.985	98.5	5.06	101	10.4	104	101	486	97.2	772	103	1020
6486_004	0.985	98.5	5.06	101	10.4	104	101	486	97.2	772	103	1020
6486_005	0.985	98.5	5.06	101	10.4	104	101	486	97.2	772	103	1020

Table 2. Intra Assay Quality Control Results For Analyte-01 (Human Plasma(H)).

Replicate #	Nominal Concentration of Quality Control Samples For Analyte-01		
	2 ng/mL	150 ng/mL	750 ng/mL
1	2.07	139	683
2	1.94	138	681
3	1.94	139	744
4	1.95	142	684
5	2.04	140	690
Mean	1.99	140	686
± SD	0.0622	1.52	26.8
Accuracy (%)	99.3	93.1	92.8
Precision (%)	3.13	1.09	3.85

Table 3. Inter Assay Quality Control Results (Human Plasma(H)).

Run #	Nominal Concentration of Quality Control Samples For Analyte-01		
	2 ng/mL	150 ng/mL	750 ng/mL
6486_002	1.93	146	744
6486_003	1.94	146	744
6486_004	1.94	146	744
6486_005	1.94	146	744
6486_006	1.94	146	744
6486_007	1.94	146	744
6486_008	1.94	146	744
6486_009	1.94	146	744
6486_010	1.94	146	744
6486_011	1.94	146	744
6486_012	1.94	146	744
6486_013	1.94	146	744
6486_014	1.94	146	744
6486_015	1.94	146	744
6486_016	1.94	146	744
6486_017	1.94	146	744
6486_018	1.94	146	744
6486_019	1.94	146	744
6486_020	1.94	146	744

Table 4. Quantitation Limit Results (Human Plasma(H)).

Replicate #	Nominal Concentration of Lower and Upper Limit Of Quantitation Samples For Analyte-01	
	LLOQ	ULOQ
1	0.878	952
2	0.865	1040
3	0.904	953
4	0.845	1010
5	0.856	985
Mean	0.870	990
± SD	0.0227	35.7
Accuracy (%)	87.0	99.0
Precision (%)	2.61	3.61

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Conclusion

In summary, the production of method validation reports has been automated utilizing the LCMS report writer, ALIS98, and Word97/VBA based report production module. This approach has enabled ALTA project managers to significantly reduce the time required to "roll-up" MVS result data into final report tables. In addition, the use of validated calculation subroutines within ALIS98 and Word97 templates has reduced the number of errors associated with manual data entry and calculations. Utilization of the MS Office97 suite (Word-97/VBA) will allow us to upgrade the product to Office 2000. Future efforts will be directed towards expanding the number of custom Word97 report templates and ease of use.