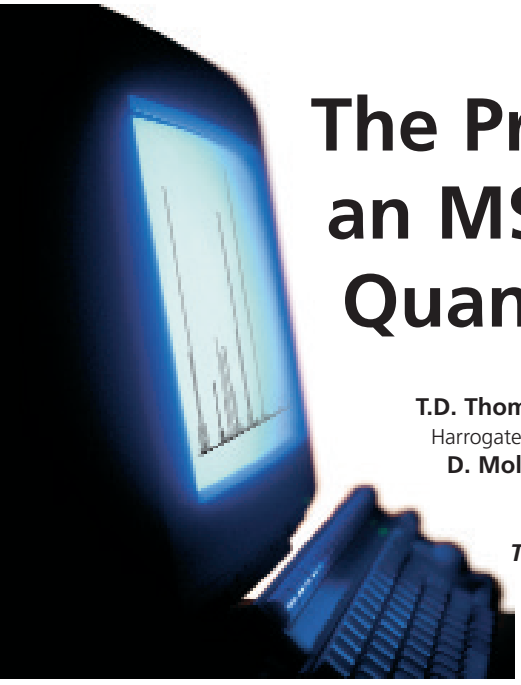

The Prospective Validation of an MS Data System used for Quantitative GLP Studies

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This article describes the prospective validation of a chromatography data system used for quantitative Good Laboratory Practice studies within a contract research organization. An outline of the overall process and the documentation produced to support the data system validation is presented.

Introduction

Computer system validation is concerned with producing documented evidence that the system in question was purchased using quality standards, was accurate when qualified and remains so throughout its operational life. The need for fully validated chromatography data systems (CDS) used for drug submissions and manufacturing has been well documented over the past few years. As the pharmaceutical and associated industries have adopted more computerized systems and begun to implement FDA rule 21 CFR Part 11, governing the use of electronic records and electronic signatures, validation of these data systems has become imperative.

Bioanalytical Services Department

The Bioanalytical Services Department of Covance Laboratories Ltd (Harrogate, North Yorkshire, UK) is part of a contract research organization that offers toxicological, preclinical and clinical analysis of biological samples from drug development studies. The work is performed in accordance with the principles of Good Laboratory Practice (GLP). For high-throughput bioanalysis, the major technique used in the department is liquid chromatography–mass spectrometry (LC–MS). Data from the analyses are eventually subjected to pharmacokinetic analysis to help determine a dosage regimen.

Validation Project Overview

This project was conducted using the life-cycle approach to validation of chromatography data systems (CDS) as described by McDowall (1–3), and consisted of three parts under a single validation plan (Figure 1).

- prospective validation of the new application software (Analyst, version 1.0) and qualification of the new associated instruments
- validation of the migration of electronic records from Macintosh systems to a Windows NT environment, as well as data acquisition on some Macintosh platforms with interpretation using Analyst software
- formal retirement of obsolete MS and Macintosh computer hardware.

This article concentrates on the first of these parts. The data migration and system retirement work has been submitted for publication separately (4).

This validation work was performed under OECD (Organization for Economic Cooperation and Development) GLP regulations (5), plus applicable sections of 21 CFR Part 11 (6). The project was facilitated by Qualify*Plus*® (version 3), a series of generic documentation specifically designed for the validation of CDS (7).

Overview of the MS Systems

The current MS equipment, software options and computing environment within Bioanalytical Services are discussed below and summarized in Table 1.

Mass spectrometry equipment: There are three main models of mass spectrometer currently operating in the Bioanalytical Services Department: API models III+, 365 and 3000 (all Applied Biosystems, Foster City, California, USA). Of these, the API III+ is obsolete because the Macintosh PC used to run the software is no longer in production. Therefore, the three systems using the API III+ mass spectrometer will be formally retired and only the API 365 and 3000 models will be used thereafter.

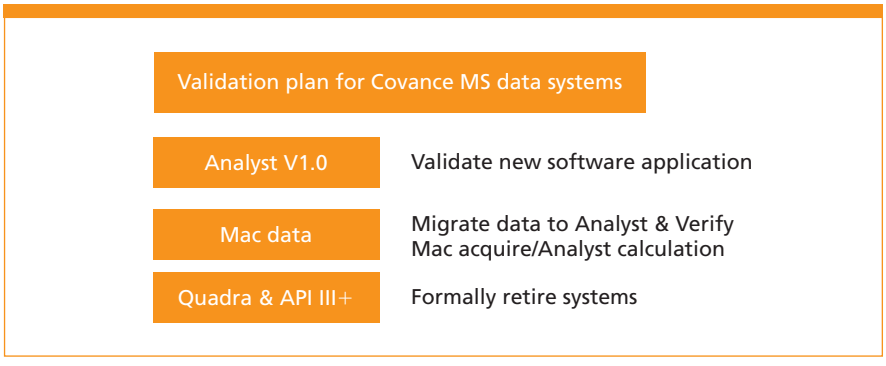

Figure 1: *Overview of the whole mass spectrometry validation, data migration and system retirement project.*

Table 1: *Data Processing Options Available in Bioanalytical Services Department.*

Mass spectrometry instrumentation	Computing hardware	Operating system	Data acquisition software	MS quantitation software
API III+	Mac Quadra	Mac OS	RAD 2.6	MacQuan 1.4
API III+	Mac Quadra	Mac OS	RAD 2.6	TurboQuan 1.0
API 365	Power Mac	Mac OS	Sample Control 1.3	MacQuan 1.4
API 365	Power Mac	Mac OS	Sample Control 1.4	MacQuan 1.4
API 365	Power Mac	Mac OS	Sample Control 1.4	TurboQuan 1.0
API3000	Dell PC	Windows NT	Analyst v1.0	Analyst v1.0

Table 2: *Intermediate Data Processing Configuration.*

Instrumentation	Hardware	Data acquisition software	MS quantitation software
API 365	Power Mac	Sample control 1.4	Analyst v1.0
API3000	Dell PC	Analyst v1.0	Analyst v1.0

Table 3: *Future Data Processing Configuration.*

Instrumentation	Hardware	Data acquisition software	MS quantitation software
API 365	Dell PC	Analyst v1.0	Analyst v1.0
API3000	Dell PC	Analyst v1.0	Analyst v1.0

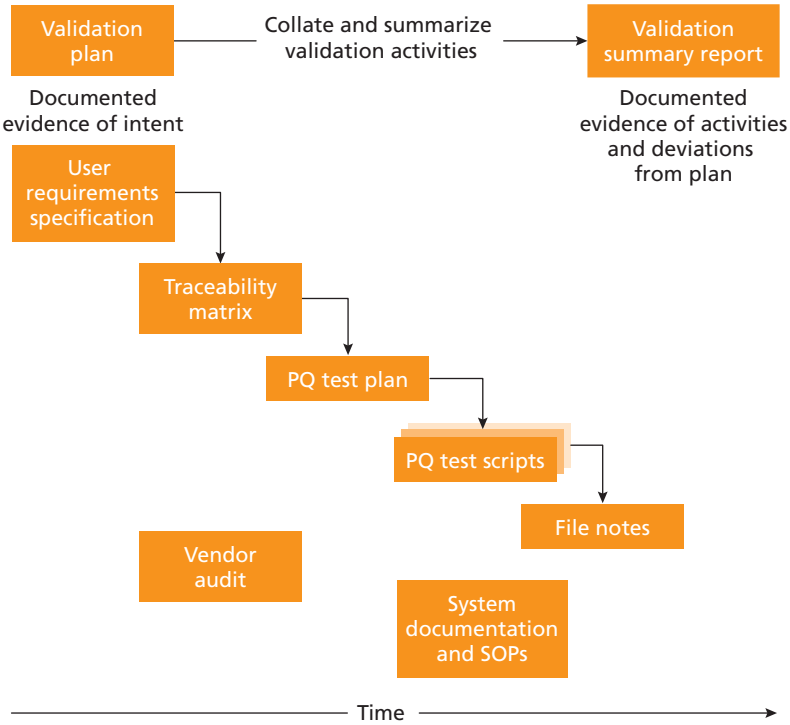

Figure 2: *Overview of the documentation for the validation project.*

Data acquisition and processing software applications: The mass spectrometer software currently used in the department is a combination of data acquisition (RAD and sample control) and data processing software (three versions) that operate in the Macintosh and Windows NT environments. The software running on the Macintosh Quadra will be retired under the work described in this article.

A mixed environment will be operated for a transition period whereby data are acquired by sample control running on a Macintosh, but all data processing and quantification are run on Analyst. In the future, after retirement of all Macintosh computers, there will be an Analyst-only environment running on the Windows NT platform.

Computing environments: The existing environment was Macintosh, with MS data being downloaded to a server following acquisition. Introduction of Analyst initiated a migration to an NT operating environment that will continue after the completion of the data migration outlined here (Table 1).

Future Configurations of MS Data Systems

In the short term, the now obsolete API III+ systems and their corresponding data acquisition and processing software (RAD 2.6, MacQuan and TurboQuan) are due to be retired in 2001–2. The API 365 systems and software will be used for the next two years or so and the data will initially be captured by Sample Control 1.4 on Power Macintosh computers and translated for subsequent processing by Analyst. Table 2 summarizes the data processing systems planned for this intermediate stage.

The long-term configuration of data systems in the department is shown in Table 3. Here the Macintosh computers and applications will be retired and only Analyst and a Windows NT environment will be used.

The Validation Process and Documented Evidence

The outline design of the Analyst validation project is represented in Figure 2. All documents were paginated, identified and controlled with sign-offs by the author with technical reviews and, where appropriate, quality assurance unit reviews. The exception was the system documentation written by the vendor; however, copies were archived as part of the preparation of the validation package of documentation. Document control and

"This project was conducted using the life-cycle approach to validation of CDS."

approval is an important requirement for internal or external audit of a computerized system validation (6, 8).

SOP for computerized system validation: The first stage was to update the existing computerized validation standard operating procedure (SOP) from one that tended to be focused on testing to a life-cycle approach. Here the validation SOP defined:

- the key roles and responsibilities of individuals involved in validation
- a life-cycle approach to validation for computerized systems within Bioanalytical Services
- a link from the life-cycle phase to the expected documentation from each stage. The intention was to define the approach for a specific system in the validation plan.

Validation plan: This document defines the intent of the whole validation effort. The format of the document is based on the Institute of Electrical and Electronic Engineers (IEEE) standard 1012-1986 (9). The key topics within the validation plan are

- to define the whole scope of the project
- to list the roles and responsibilities of individuals and organizational units
- to define the life cycle of the project (based on the department SOP) and the documentary evidence to be generated in each phase to describe how the data system will be validated
- to highlight when validation activities will be performed by reference to the project plan
- to define the meaning of signatures; here a section outlines the role and responsibility for individuals who are signing documents generated under the validation plan
- to outline the reporting and administrative requirements for the project.

This document was written early in the validation of Analyst as it permits forward planning of deliverables called for under the plan. Writing this later in the project means that documents may have to be written retrospectively and this could delay the project.

System specification and selection: If a new system were being specified, a full system specification and selection process would be performed. However, in this instance, the existing system was being made obsolete and a new system from the same vendor being implemented; therefore, no system selection was performed. A user requirements specification (URS) was written for the system and used as the basis of the validation. This was accompanied by the purchase order and delivery notes associated with the system as evidence of the specification stages of the project.

The URS defines the functions that users of the data system have selected for validation, and was written after consultation with the MS users. The main sections of the document were

- overall system requirements
- build acquisition method
- acquisition batch
- instrument control
- data acquisition
- data files and electronic signatures
- chromatography data: display and interpretation
- calibration
- system suitability test parameters
- calculations
- reporting and collation of results
- interfaces to spreadsheets or laboratory information management systems.

Where appropriate, 21 CFR Part 11 (6) features for data file integrity, security and audit trail were specifically defined in the URS so that they could be tested under the performance qualification (PQ) section of the validation. In addition, the users also prioritized each feature as mandatory (M), highly desirable (H) or nice to have (N). Figure 3 illustrates some typical requirements in the URS for some features associated with raw data (electronic record definition), electronic signatures and audit trail. Note that each requirement is

• Raw Data Definition for the Data System

The format of the raw data from the system is defined in this section.

DS Reference	Raw Data Feature and Specification	M/H/N
DS 7.1	The raw data for the DS are defined as the electronic data files, together with the acquisition method and batch files used for an individual analytical run	M
DS 7.2	The data file must ensure integrity through the use of check sums or equivalent and not be capable of alteration by the use of a text editor or equivalent application	M

• Electronic Signatures

The following features are considered the minimum to support electronic signatures under 21 CFR 11.

DS Reference	Raw Data Feature and Specification	M/H/N
DS 8.1	The DS will need to be classified and operated as a closed system under 21 CFR 11	M
DS 8.2	A unique combination of password and user ID must be used to log on and approve actions and results as an electronic signature	M

• Raw Data Definition for the Data System

DS Reference	Raw Data Feature and Specification	M/H/N
DS 9.1	A configurable audit trail should be available allowing the use of defined functions to trigger different levels of auditing	H
DS 9.2	An audit trail should be available to support a compliant operation during audit without any major work-up	M
DS 9.3	The audit trail should be able to track the history (raw data to reported results) recording functions, users, date, time and reason for change	M

Figure 3: *Example from URS relating to Part 11 requirements.*

uniquely numbered and prioritized as this leads into the next stage of the process — the traceability matrix.

Traceability matrix: This links the URS to the actual testing outlined in the PQ test plan. It outlines how the requirements of the Analyst LC–MS data system software defined in the URS will be qualified, as only mandatory requirements were considered for PQ testing. Specifically, this document states if an individual function within the URS will or will not be tested; if it is to be tested it highlights the test script number under which it will be tested.

Vendor audit and report: The audit of the software development portion of the system development life cycle is an essential part of the validation project for critical systems. As outlined under the Good Automated Manufacturing Practice guidelines (10) a configurable software package is audited to ensure that the software development is consistent with the production of a quality product. For Applied Biosystems, this was conducted remotely through a vendor audit questionnaire supplied by the Covance quality assurance department to be consistent with the company's policy on vendor audits. The replies received from the vendor were used to underwrite the system development portion of the system life cycle.

Table 4: *Analyst Software Features to be Tested in each PQ Test Script.*

Test script	Component/module	Feature
1	Security and access control	Demonstrate access to the system and features by different levels of authorized user.
2	Year 2000 compliance	Historical data was generated in 1999 and used to show that the Analyst software could handle date changes as defined in PD 2000-1.
3	Data file integrity	Checking that the system could test for invalid records to meet 21 CFR Part 11 requirements.
4	Back-up and recovery	Back-up and recovery of individual data files, analytical runs and projects from the normal back-up media.
5	Archive and restore	Data was archieved on to a long-term medium, then restored and reprocessed to confirm they were identical to the original.
6	Instrument control	Instrument control of key equipment interfaced to the software including the ability to control different autosampler injection racks.
7	System capacity: Number of analytes	Ability of the software to cope with an assay involving five separate analytes.
8–10	Calibration methods	The calibration algorithms used were checked for correct function within these scripts. System capacity, dilution range and common problems were also included to confirm that they worked over the required ranges.
11	Integration algorithms	The algorithms used for intergrating the peaks were assessed to see that they produced similar results to manually calculated areas and heights.
12	Smoothing algorithms	Smoothing algorithms can be used to improve a peak shape and were checked to confirm that they worked correctly.
13	Data reprocessing over the network	Data acquired by one instrument were reprocessed on a processing client to see if the same results were obtained.
14	Deviation of the internal standard	Calculation of the mean and standard deviation of the internal standard peak area against an external package.
15	Auto and manually processed peak	Confirmation that manually and automatically processed peaks can be distinguished.
16	Audit trial	Audit trail comments conform to current principles of GLP and 21 CFR Part 11.
17	Export to Excel	Export of results into Excel was investigated to confirm this works as anticipated.
18	Calculation of disk space remaining	Confirmation that there was enough disk space available was checked before a run started.

Installation qualification (IQ): The correct installation of the mass spectrometer, associated equipment, and computer hardware and software is documented under this stage of the validation process. The IQ material from the vendor was used after evaluation (although considered basic in comparison with other IQ packages), as it concentrated on the installation of the equipment rather than the system as a whole, but it was deemed adequate for the purpose. Verbal suggestions for improvement were made to the vendor for later releases of Analyst.

Operational qualification (OQ): This phase of the life cycle should document that the installed system operates through its anticipated operational ranges; however, as the vendor did not provide any package for OQ this phase was not performed. This resulted in more emphasis being placed on the performance qualification and vendor audit.

Performance qualification (PQ): The PQ test plan defines the system to be tested and highlights the features to be tested against the URS functions. Just as importantly it defines those features, such as the operating system and any specific functions in the application software not used (e.g., calibration methods). For the testing, a number of assumptions, limitations and exclusions were defined and discussed as part of this plan. This is important as it allows contemporaneous notes to be written of the test approach.

The features to be tested were divided across a suite of 18 test scripts. Some of these test scripts were intended to be executed on their own, such as security and access control. However, some test scripts were linked together so that one test script would be used to generate data, calibrate the method and calculate the final analyte concentration. The data generated under the first test script could then be used for testing back-up and recovery under a second test script. Some test scripts in the suite could not be executed until after others had been completed; these interdependencies were noted in the respective test scripts. For example, the reprocessing test script 13 could not be run until data were acquired under test scripts 8–10.

PQ test scripts: The PQ test scripts describe in detail the tests of the key functions as defined in the PQ test plan. Each test script is a self-contained document with all the instructions needed to execute the whole script. Table 4 lists the test scripts that were prepared and executed for this validation.

Within each script there are several test procedures, each testing one or more functions of the software in the way that Bioanalytical Services uses the system. Within a test script are a number of test procedures for specific function testing that consist of a number of test steps. Each test step has expected results against it and space for the observed results when the script is executed. At the end of each test procedure, the documented evidence is collated and the test results compared with predefined acceptance criteria to see if they have passed or failed. At the end of the script is a summary log and a statement detailing whether the test script has passed or not.

SOPs and system documentation: The system documentation provided by the vendor was evaluated. Generally it was well written but there were instances where functions defined in the manuals were not in this version of the released software, such as data export in Excel format and cubic line fit for calibration curves. These were noted in the validation summary report. Consequently, more emphasis was placed on user training and SOPs; the latter was listed and summarized in the appropriate section of the validation summary report.

"Each test script is a self-contained document."

User training: Two key users went on a vendor-training course and, using a cascade approach, these people became trainers to the rest of the laboratory users; all training records were updated accordingly. Where there were 21 CFR Part 11 non-compliances, the procedural controls were included in the training.

Validation summary report: Summarizes the whole life cycle of the CDS and discusses any deviations from validation plan and quality issues found. This document gives management authorization to use the system and summarizes in detail each phase of the validation life cycle for the Analyst software.

The results of this portion of the validation project showed that the system was fit to be released for general use; however, the software was found deficient in certain areas. Many features of the system did not perform as perceived when the URS, test plan and scripts were written and as such led to conditional passes. The reasons for conditional passes were minor and did not have any major impact on the system performance. The tests that fell into this category were

- security access and control
- calibration: linear regression and quadratic line fit
- integration algorithms
- calculation of disk space remaining.

Four test scripts were unable to be run as written or were found to refer to system functions that were not available for the current version and, as such, were not run or deferred until a later date. The following test scripts fell into this category:

- archive and restore
- calibration: cubic line fit
- deviation of the internal standard
- audit trail comments.

The issues were documented in file notes and discussed in the validation summary report under deviations from the plan and their impact on the overall validation and quality of the system evaluated. For all the points here there was

little impact on the overall quality of the system as either a workaround could be found or the issue was not a major one.

As part of the validation summary report, non-compliance details with 21 CFR Part 11, such as the audit trail only starting during the quantification of analyte concentration and not during the acquisition of data, and the ability to overwrite files with little if any warning were listed. These issues were communicated to the vendor for incorporation in a new version of the software.

The final section of the validation summary report is a list of all documentation associated with the project and a statement of operational release of the system.

Summary

This work described the validation of an MS data system that incorporates testing for 21 CFR Part 11 features. The version tested is not compliant with the requirements of the regulation but with procedural controls that can provide a compliant operation until a technically complaint version of the software becomes available.

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