

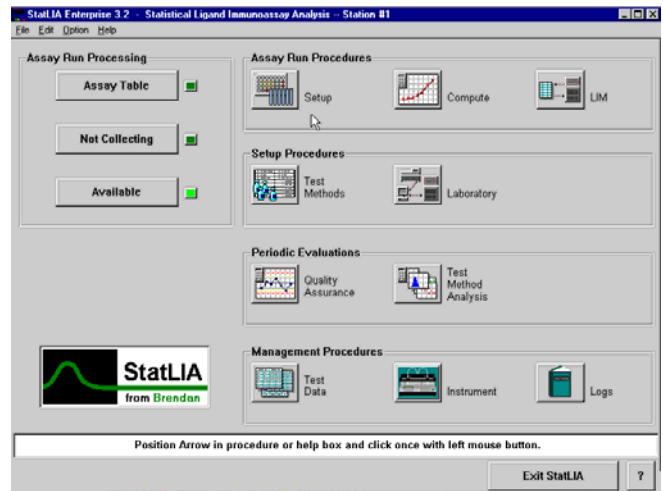
BrendanScientific
TRUE STATISTICAL RELIABILITY

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StatLIA®

Validation Package

To validate StatLIA 3.2, Brendan offers a Validation Package that includes User Requirements, Installation and Operational Qualification (IQ/OQ) Protocol, and a Trace Matrix to link the test cases with the user requirements. The package also includes additional IQ/OQ Protocols to validate instrument interfaces and secondary workstations. The test cases in the Validation Package verify that the software has been installed correctly, that it is operating according to the user requirements, and that the mathematical computations are accurate. The Validation Package was designed to help customers meet current regulatory requirements of the FDA and European regulatory agencies.



DOCUMENTS / CD-ROM



The Validation Package includes a printout of each document for immediate execution. The documents are also available in electronic form. The validation CD includes all of the necessary test and data files to execute the IQ/OQ Protocols. To verify the mathematical computations performed by StatLIA 3.2, Brendan used Mathematica 5.0, a general purpose symbolic and numerical mathematical computational program developed by Wolfram Research, Incorporated. The output files from Mathematica are also included on the Validation CD. The package also includes a StatLIA 3.2 Validation Certificate.

EXECUTION ASSISTANCE

Brendan has formed a strategic partnership with Validation Technologies Inc.®, an ISO 9001:2000 certified validation company. VTI has trained validation engineers to assist in the execution of this Validation Package or other validation requirements that may be needed. VTI has acknowledged expertise in validating systems used in the healthcare industries regulated by the FDA and the European equivalent agencies, including laboratory and manufacturing systems used in support of cGMP, GLP and GCP work. To reach Validation Technologies Inc., call 800-930-9222 or visit their Web site at www.validation.org.

PROTOCOL EXCERPTS

For further information, excerpts of the Validation Package are available.

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USER REQUIREMENTS		Page 4 of 15

5.3 Security Control

5.3.1 Assigning Passwords

The system shall allow an administrator the ability to assign individual users a password to access the system.

5.3.2 Establishing User Levels

The system shall allow an administrator the ability to establish multiple access levels to enable or deny access to different users.

5.3.3 Restricting Display of Passwords

The system shall not display the user's password in the password entry dialog box.

5.3.4 Change Password Identification

The system shall allow the user to change their password when they are prompted to enter their password in the Password Entry Dialog Box.

5.3.5 Assigning Unique User Identification

The system shall allow an administrator the ability to assign unique login names for all users.

5.3.6 Identifying Users Uniquely

The system shall disallow the same login name to identify users.

5.3.7 Restricting System Module Access (Check Points)

The system shall allow an administrator the ability to restrict access to system modules via check points that are assigned user access levels.

5.3.8 Activating or Deactivating Security Check Points

The system shall allow an administrator the ability to control access to individual system functions.

5.3.9 Selecting Check Points for the Security Log

The system shall allow an administrator the ability to select the functions in which to record activities in the Security Log.

5.3.10 Entering Password Aging Days

The system shall allow an administrator the ability to enter the number of days before a user is required to change their password.

Note: This IQ/OQ Protocol is to be completed in accordance with the StatLIA 3.2 Validation Instructions.


Test Case Instructions	Expected Results	Pass/ Fail	Initial & Date
Test Case 7: Password Aging			
Click on Security Parameters and type in <Admin1> for Name and <admin0> for Password in the Password Entry box.	Admin appears in the Name field. Xxxxx appears in the Password field. Security Parameters Setup appears.		
Verify Password Aging is not set to 1.	0 appears in the box.		
Enter 1 in the Password Aging box.	1 appears in the box.		
Click Save to return to Laboratory Setup screen.			
Click Cancel.	StatLIA 3.2 main screen appears.		
Click Exit StatLIA.	StatLIA 3.2 process is stopped.		
Go into the system clock and move the day forward 1 day.	Workstation calendar day is 1 day ahead.		
Double click StatLIA 32 icon from desktop.	Password Dialog box appears.		
Enter <User> Name and <user> password in Logon Dialog box.	Message comes up that password has expired.		
Click OK.	Change Password dialog box appears.		
Enter a new password and confirm with the same entry.	StatLIA 3.2 main screen appears.		
Test Case 8: Registered User			
Click Laboratory → Security Parameters (type in <Admin1> for Name and <admin0> for Password in the Password Entry box).	Security Parameters Setup screen appears.		

Verification

Your signature indicates the information recorded on this page by the tester(s) of the protocol has been reviewed by you for accuracy and completeness, and any associated documentation has also been reviewed for accuracy and completeness.

Note: Use this document in conjunction with the User Requirements Document and IQ/OQ Protocol.

Number	User Requirements	Requirement Identifier	Test Case No.
1	Workstation Operating Environment	5.1.1	1
2	StatLIA Files	5.1.2	1
3	Launching StatLIA	5.1.3	1
4	StatLIA Documentation	5.1.4	N/A
5	Test Data Conversion	5.2.1	2
6	Archive Conversion	5.2.2	3
7	Log Data Conversion	5.2.3	17
8	Assigning Passwords	5.3.1	4
9	Establishing User Levels	5.3.2	4
10	Restricting Display of Passwords	5.3.3	4
11	Change Password Identification	5.3.4	6
12	Assigning Unique User Identification	5.3.5	4
13	Identifying Users Uniquely	5.3.6	4
14	Restricting System Module Access (Check Points)	5.3.7	5,9
15	Activating or Deactivating Security Check Points	5.3.8	5
16	Selecting Check Points for the Security Log	5.3.9	5
17	Entering Password Aging Days	5.3.10	7
18	Entering Registered User Time	5.3.11	8,9
19	Preventing Original Data from Being Overwritten	5.4.1	16
20	Encrypt Data Files and Logs	5.4.2	14
21	Time-Stamping Records	5.4.3	17
22	Storing Raw Data from Input Source/Data Detector	5.4.4	11
23	Secure Raw Data	5.4.5	16
24	Preventing Invalid Data from Being Entered	5.4.6	15
25	Curve Fitting Options	5.5.1	10
26	Types of Standard Curve Tests	5.5.2	10
27	Plot Mean or Normalized Response	5.5.3	10

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VALIDATION INSTRUCTIONS		Page 1 of 14

1. PURPOSE

This validation instruction document describes the required activities, documentation and instructions for the validation of StatLIA 3.2 that will demonstrate proper installation, operation and performance, and comply with user requirements.



Prior to release, StatLIA 3.2 has gone through a rigorous development, testing, and functional validation process at Brendan Technologies, Inc. (Brendan). This validation instruction document will provide the necessary information so that the software user can validate StatLIA 3.2 in the end user environment.

Three separate protocols make up the validation of StatLIA 3.2: (1) Installation and Operational Qualification protocol (IQ/OQ), (2) Secondary Workstation qualification, and (3) the Instrument Driver qualification protocols. The requirements pertaining to these protocols can be found in the attached User Requirements document. A trace matrix is also included that maps the relation from requirements to the test cases in the protocol. Each individual user environment will dictate which protocols are necessary to validate StatLIA 3.2. The StatLIA 3.2 interfacing / networking configuration diagrams in Section 5.2 can be used to help determine if secondary workstation or driver qualification protocols are needed.

The IQ section of the Installation and Operational Qualification protocol will verify that the correct hardware and software are available in the user environment to run StatLIA 3.2. The OQ section will verify that StatLIA 3.2 functions adequately and in accordance with the User Requirements. The OQ also will verify that StatLIA 3.2 can correctly perform the mathematical analysis of the collected data.

The mathematical computations used in StatLIA 3.2 are comprehensive, and specifically designed for the numerically intensive requirements for computing and statistically analyzing non-linear dose-response data. StatLIA 3.2 uses many complex advanced algorithms that cannot be as easily reproduced in traditional statistical and spreadsheet programs. To verify the mathematical computations performed by StatLIA 3.2, Brendan used Mathematica 5.0, a general purpose symbolic and numerical mathematical computational program developed by Wolfram Research, Incorporated. The StatLIA 3.2 algorithms were computed in Mathematica to generate output, which was used as a reference standard to compare against the output from StatLIA 3.2. The Mathematica output (provided as Adobe .pdf files) and Mathematica notebook (.nb) files used to generate the output are provided in this Validation Package. The notebook (.nb) files can be re-executed using Mathematica 5.0. Some of the mathematical computations used in StatLIA 3.2 are detailed in the following manuscripts:

- Gottschalk, PG and Dunn, JR; *Measuring Parallelism, Linearity and Relative Potency in Bioassay and Immunoassay Data*; The Journal of Biopharmaceutical Statistics (in press).
- Gottschalk, PG and Dunn, JR; *The Five Parameter Logistic: A Characterization and Comparison to the Four Parameter Logistic*; (submitted for publication).

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- Gottschalk, PG and Dunn, JR; *Determining the Error of Dose Estimates and Minimum and Maximum Acceptable Concentrations from Nonlinear Dose-Response Curves*; (submitted for publication).

2. SCOPE

This validation package is intended for the end user validation of StatLIA 3.2. StatLIA 3.2 is an integrated application software system that is used to collect the colorimetric, fluorometric, chemiluminescent, isotopic or other raw data from an analytical detector and analyze the dose response-related data. The complex functionality of the software works via a number of integrated modules, each of which represents a series of interconnected functions.

StatLIA 3.2 is based upon the incorporation of software change requests into the architecture and code of StatLIA 3.1. These changes were verified by Brendan as part of the Software Change Request process and Software Development Life Cycle.

- 2.1 The validation of StatLIA 3.2 will encompass the following sections found in the User Requirements document:
- 2.1.4 Installation
 - 2.1.5 Data Conversion
 - 2.1.6 Security Control
 - 2.1.7 Electronic Records Compliance
 - 2.1.8 Variable Settings for Different Test Methods
 - 2.1.9 Variable Settings for Different Assays
 - 2.1.10 Assay Computation and Recomputation
 - 2.1.11 Assay Reports
 - 2.1.12 Data Exportation – Output
 - 2.1.13 Saving and Reviewing Raw Data
 - 2.1.14 Log Reports
 - 2.1.15 Networked Files and Workstations
 - 2.1.16 Assay QC Computation

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2.1.17 Curve Fitting and unknown Concentration Computations

2.1.18 MinMax DC Computation

2.1.19 Parallelism Computation

2.1.20 Test QA Computation

2.1.21 Weighting Computation

2.2 The User Requirements are mapped to the following test cases, as indicated in the Trace Matrix:

Operational Test Cases

2.2.1 Operating Environment

2.2.2 Convert Test Data Files

2.2.3 Convert Archived Test Data Files

2.2.4 Administer User Permissions

2.2.5 Administer Security Parameters

2.2.6 Change Password

2.2.7 Password Aging

2.2.8 Registered User

2.2.9 Administrator Detectors

2.2.10 Administer Test Method

2.2.11 Setup Assay



2.2.12 Compute New Assay

2.2.13 Export Unknown Results

2.2.14 Review Stored Assays

2.2.15 Recompute Old Assay

2.2.16 Secured Raw Data

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2.2.17 Security Log

2.2.18 Error Log

2.2.19 Assay Log

2.2.20 LIM Release Log

Assay Quality Control Computation

2.2.21 Mean, Standard Deviation of Reference Set

2.2.22 T Statistic, and T Probability of Comparison of Reference Set to Current Assay

2.2.23 F Test of Expected Variance to Actual Variance

Curve Fit and Unknown Concentration Computations

2.2.24 Adjusted and Normalized Response Computation and Average the Replicates

2.2.25 Fixed Weight Computation in the Adjusted Case

2.2.26 Fixed Weight Computation in the Normalized Case

2.2.27 Unweighted weight computation

2.2.28 5PL Fitting Algorithm for Ascending, Adjusted Data

2.2.29 5PL Fitting Algorithm for Descending, Normalized Data

2.2.30 4PL Fitting Algorithm for Ascending, Adjusted Data

2.2.31 4PL Fitting Algorithm for Descending, Adjusted Data


2.2.32 Single Dilution Concentration Computation Using a Logistic Curve

2.2.33 Linear Regression Fitting Algorithm in Normalized Case, Fixed Weight

2.2.34 Linear Regression Fitting Algorithm in Normalized Case, Unweighted

2.2.35 Single Dilution Concentration Computation Using a Linear Curve

2.2.36 Single Dilution Concentration Computation Using an Ascending Cubic Spline Curve

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- 2.2.37 Single Dilution Concentration Computation Using a Descending Cubic Spline Curve
- 2.2.38 Single Dilution Concentration Computation Using an Ascending Point-to-Point Curve
- 2.2.39 Single Dilution Concentration Computation Using a Descending Point-to-Point Curve
- 2.2.40 Weighted Dilution Concentration using Multiple Dilution Concentration
- 2.2.41 One Standard Method
- 2.2.42 Pos/Neg Using $B/Nk_1 + Pk_2 + k_3$ Cutoff Formula
- 2.2.43 Pos/Neg Using $B/N + 95\%SD$ Cutoff Formula
- 2.2.44 Blank Concentration
- 2.2.45 Blank Response
- 2.2.46 Concentration Confidence Limits for 5PL
- 2.2.47 Concentration Confidence Limits for 4PL

MinMaxDC Computation

- 2.2.48 Minimum-Maximum Detectable Concentration Range Algorithm
- 2.2.49 Minimum-Maximum Acceptable Concentration Range Algorithm for 5PL
- 2.2.50 Minimum-Maximum Detectable Concentration Range Algorithm for 4PL

Parallelism Computation

- 2.2.51 5PL Parallelism Algorithm
- 2.2.52 4PL Parallelism Algorithm
- 2.2.53 5PL Relative Potency Confidence Limits Algorithm
- 2.2.54 4PL Relative Potency Confidence Limits Algorithm

Test Quality Assurance Computation

2.2.55 Quality Assurance Statistical Algorithms: ANOVA, F Probability, T Test, T Probability, and Confidence Limits

Weighting Computation

2.2.56 Weighting Algorithms Within/Between ANOVA

2.2.57 Best Fitting Power Curve Using a Log-Log Linear Regression

3. REFERENCES

- 3.1 StatLIA 3.2 User Requirements Document
- 3.2 StatLIA 3.2 Installation Qualification/ Operational Qualification Protocol
- 3.3 StatLIA 3.2 Driver Qualification Protocol (optional)
- 3.4 StatLIA 3.2 Secondary Workstation Qualification Protocol (optional)
- 3.5 StatLIA 3.2 Trace Matrix Document
- 3.6 StatLIA 3.2 Operator's Guide
- 3.7 StatLIA 3.2 Reference Manual

4. TERMS AND DEFINITIONS

For the purpose of this document, the following terms and definitions will apply:

Term	Definition
IQ	Installation Qualification
OQ	Operational Qualification
Trace Matrix	A table showing the relationship of User Requirements to Test Cases
SDLC	Software Development Lifecycle
Tester	Person responsible for executing the protocol.