Parallel-Line and Parallel-Logistic Assays

Biological or potency assays are frequently analyzed with the help of the parallel-line or parallel-logistic (3-, 4- or 5-parameter fit) methods. These methods have major advantages over traditional single-point assays:

- The linear or sigmoidal dose-response correlation is not only assumed but confirmed in each calculation. Testing can be done either by difference/hypothesis testing or by similarity/equivalence testing, which was newly introduced by the US Pharmacopeia chapters <1032>, <1033> and <1034>.
- The dose-response curves of the standard and sample preparations are confirmed to be parallel. Whereas in single-point analysis parallelism is a necessary requirement too, but cannot be proven.
- A dose-independent potency in terms of the standard’s potency is calculated for each assay, and its validity is statistically proven.

The complex statistical analysis of these methods requires an advanced software solution to be easy, flexible and efficient. This is the mission of our PLA 2.1.

Today’s Requirements for Advanced Assay Analysis Software

Statistics - Support of EP 5.3 and USP <1032>, <1033> and <1034>

An advanced assay analysis software delivers state-of-the-art statistical methods, allowing fast and efficient assay analysis. The statistics used should be in accordance with the international guidelines, especially in accordance with the European Pharmacopoeia chapter 5.3 and the new US Pharmacopoeia chapters <1032>, <1033> and <1034>. Does your software allow to analyze according to both standards?

Regulatory Requirements

However the requirements do not end up with statistics. The requirements are much beyond efficient data analysis. Your software should fulfill the regulatory requirements (e.g. GLP, GAMP, FDA’s 21 CFR part 11 and other international or local needs). The software vendor has to offer solutions for validation. Does your software support advanced security features, audit trails, direct support of IQ / OQ / PQ tasks?

How is data being protected from manipulation by technical errors or mistakes?

Transfer Data Between Projects, Sites and Companies

One of the most difficult tasks today is the transfer of your assay between different sites of your company, to and from contract research organizations or simply between different project stages.

Do you use software that can easily be validated when your project reaches advanced stages? Does your software support a validated transfer of data to other sites or service providers (e.g. CROs)? Is your analysis independent of your data acquisition systems software? Is it open to integrate with other acquisition software or target systems?
FEATURES

BASICS FEATURES
- Easy calculation of parallel-line and parallel-logistic statistics
- PLA 2.1 is easy to learn, easy to use and to deploy
- Smart design supports daily tasks
- Set up templates to define your protocol
- Ad-hoc data analysis: Explore your assay directly on the screen
- Advanced Data Management: Assay data is organized in databases for fast and secure access. Set up any number of databases and share your data across the network.
- Assay documentation features allow you to document necessary meta data.
- Secure reporting. Standard calculation reports are created as secured Adobe PDF files. Report Templates for Microsoft Word and Excel are also available.
- Technical and scientific support by Stegmann Systems

INTEGRATION FEATURES
- A large number of optional Import Modules is available to connect your acquisition system to PLA.
- PLA’s Enhanced Import Modules are able to execute even complex calculations on your input prior to setting up an assay inside PLA.
- PLA’s Enhanced Reporting System is able to report to virtually any target system (e.g., LIMS, Office)

FIT FOR THE ENTERPRISE
- PLA focuses the whole life cycle of assay development. You achieve maximum flexibility during development and maximum security when your assay reaches the production state.
- Electronic Signatures qualify your data records
- Digital Signatures using cryptographic tokens secure the integrity of your data records
- 21 CFR part 11 compliance, GAMP level 3 (commercial off-the-shelf software)
- A Validation Package is available. The extensive IQ, OQ and PQ tasks are automated.
STANIMAL FEATUES AND DATA MANAGEMENT

FLEXIBLE ASSAY SETUP

PLA allows you to define your assays very flexible. Define standards, samples, control samples and controls with up to 25 treatments and replicates. Optionally define the preparation of your stock solution or start at the raw material/bulk substances. Define any pre-dilution factors. Define any dilution scales. Assume standards and samples equipotent or assign a stated/labeled potency to your samples. PLA automatically performs the corresponding back-fit calculations for your system.

CONFIGURATION

While the parallel-logistic assay (full curve fit) describes the whole dose-response correlation, parallel-line assays focus the significant part of the dose-response relationship. PLA is able to locate the significant parts of the dose-response correlation automatically. There is a full featured range of control options to determine the optimal assay configuration.

CURVE FITTING

PLA implements both Parallel-Line Assays and Parallel-Logistic Assays (3-, 4- and 5-parameter sigmoidal functions). For all models transformation functions for the response values are available to reduce heteroscedasicy.

The 3-parameter logistic curve fit is a constraint 4-parameter function, where either the lower or the upper asymptote is bound to a fixed value, which can either be given or derived from the control lines. This allows truncated data to be analyzed.

OUTLIER DETECTION

The Studentized Residuals Method, Dixon Test, Grubb’s Test and a test based on the standard deviation are available to exclude outliers from the analysis. Outlier Tests may be applied once or in a recursive manner.

ANALYSIS OF VARIANCE (ANOVA)

PLA is fitted with two variants for the Analysis of Variance of the fitting results are available. Standard confidence intervals or confidence intervals according to Fieller are calculated.
ADVANCED TESTING FUNCTIONALITY

PLA 2.1 supports 32 different classes of tests for your assay system. You are free to choose and combine any of these tests to fit your assays need. Select the tests that describe your system best. You can mix up any kind of tests.

Examples:

- Very precise assays tend to fail linearity in hypothesis testing. You are free to decide whether a hypothesis based linearity test is conducted or you set the severity level of the test to informative, leading the overall result not to fail.
- In transition from difference testing to similarity testing according to the USP you can setup your assay system to fulfill both: difference/hypothesis testing and similarity/equivalence testing meeting all the requirements at once. This is also helpful when you are starting to develop equivalence margins.

AVAILABLE TESTS

- 5 different hypothesis tests for regression, linearity, parallelism
- 23 different equivalence tests for all plain parameter estimates, differences, ratios and scaled differences of parameter estimates as well as for the asymptote range and ratio.
- Other tests: number of outliers, relative potency, relative potency range etc.

ASSAY AND SAMPLE SUITABILITY TESTS / ASSAY CONTROLS

Define any test to serve as either an assay suitability test or as a sample suitability test with the power to fail a single sample or the whole assay. Set up assay controls with well known data to serve as assay controls.

SEVERITY LEVELS

You can set up any test any number of times to implement different information, warning and error limits for your system.

POTENCY CALCULATION

Depending on the setup your calculation starts at the bulk substance, stock solution, or at the dilution scale level. Various types of potency factors are calculated directly (e.g. assigned, assumed or labeled potencies of your standard or your sample).

COMBINATION OF ASSAY RESULTS

For the calculation of reportable values PLA is fitted with the weighted and unweighted combination calculation of assay results according to the European Pharmacopoeia and the US Pharmacopeia.
FIT FOR THE ENTERPRISE

VALIDATION AND GXP COMPLIANCE
According to GAMP software has to be validated on the customer’s computer system. The software vendor is only able to verify the software in his labs. The optional Validation Package helps you to manage the tasks of installation qualification, operational qualification and performance qualification (IQ, OQ, PQ) fast and efficiently.

INTEGRATION
PLA has a full set of interfaces for the import of raw data from data acquisition systems, for the export of assay data to e.g. documentation systems and for the reporting into many target systems (e.g. Adobe Acrobat PDF™, Microsoft Excel™, Microsoft Word™, OpenDocument). Individual modules can be created at low cost.

TRANSFER OF DATA AND TEMPLATES
PLA allows to transfer data and templates between projects, sites and companies in a secure manner.

The trustability and integrity of the data is assured by a combination of electronic signatures, that are preserved in the transfer, and cryptographically secured data transfers. PLA secures the information with the help of its own integrated PKI (Public Key Infrastructure). This operation is completely transparent for the user. It assures the secure communication of data and templates to different projects, sites or CROs.

ROLES AND PERMISSIONS
PLA comes with its own permission system. The user is assigned a typical role that gives him a specified access level to the project’s database. PLA differentiates Administrators, who are responsible for a PLA installation or database, PLA Users and PLA Inspectors. The latter are allowed to review data only.

TEMPLATES
PLA comes with a template engine for assays and methods. Templates can be defined on the user level or as mandatory templates. The administrator can prohibit the manipulation of sets of properties (e.g. method details) from manipulation by the user. In this manner you can realize standard operating procedures (SOPs) within PLA. Templates can also be signed electronically.
21 CFR PART 11 COMPLIANCE

ADVANCED SECURITY FEATURES

In accordance with the FDA 21 CFR part 11 PLA has its own security infrastructure that requires users to log into the system. User accounts and their roles are defined with an easy-to-use interface. The accounts and their roles are database specific. In addition to this account management PLA is fitted with the full range of security options required by the 21 CFR Part 11. The PLA Administrator can define security policies for each database in accordance to regulatory or your company's need. The feature includes password complexity, password aging, password blocking and password history rules. You may also define inactivity locks to prevent from unauthorized access to the system.

ELECTRONIC SIGNATURES

Electronic Signatures can be applied to PLA's records. The application of electronic signatures is a requirement of the 21 CFR part 11. With PLA advanced data storage technology electronic signatures can even be moved between different installations of PLA (e.g. between your CRO and your company).

AUDIT TRAIL

PLA has its own Audit Trail that covers all changes of data and properties of your assay and of all security features inside PLA. The audit trail can be inspected on a per-database and a per-assay level.

DIGITALLY SIGNED ELECTRONIC RECORDS

PLA benefits from the XML industry standard for the storage of electronic records. This very flexible format has the main advantage that it is human readable, which is another requirement for compliance. PLA makes use of the XML Signature 1.0 Industry standard to assure the integrity of all the data that PLA works with. The XML Signature Standard applies a digital cryptographic signature to each data package. With the help of this signature the integrity of the electronic records is checked every time PLA makes use of them. This integrity check prevents any unauthorized or unwanted data modification, e.g. by computer defects.
PLA 2.1 SYSTEM: OPTIONAL COMPONENTS

The main component of the PLA system is the PLA 2.1 Base System. This package is fully featured and allows you to calculate and manage your assays. PLA 2.1 is able to deeply integrate into your environment. In addition several optional components are available for PLA. (These components are licensed once per site. If licensed they are available for all PLA installations on your site without additional charges). All Optional Components are automatically included in the Validation Package Installation Qualification process.

PLA VALIDATION PACKAGE

The PLA Validation Package consists of extensive documentation and software. It contains the complete documentation of the Installation Qualification, Operational Qualification, Performance Qualification (IQ, OQ, PQ), and descriptions of the development process, certificates of quality, a 21 CFR part 11 statement. The IQ, OQ and PQ tasks are automated. The installation qualification and operational qualification with vendor data takes only minutes, and certificates of qualification are being generated automatically.

PLA IMPORT MODULES & EXPORT MODULES

PLA Import Modules connect PLA with your data acquisition software. They are currently available for over 50 different data acquisition systems. Export Modules are able to connect PLA to other systems. Missing formats are developed on demand.

PLA UPGRADE PROTECTION

Every product is covered by a 12-month PLA Upgrade Protection (Software Maintenance Contract) which is automatically included with every purchase. When the PLA Upgrade Protection is about to expire, you receive a quote without obligation to extend the period for another year. PLA will continue to work without a software maintenance contract.

SYSTEM REQUIREMENTS

- 300 MB of free disk space.

The retail version of PLA is delivered with a hardlock device that has to be attached to a USB port of your computer systems when PLA is running. Concurrent use licenses are available. PLA is Terminal Server aware (concurrent use licenses required).

- Microsoft JET 4.0 Engine (max 3 concurrent users)
- Microsoft SQL Server 2000 or higher

14-day Trial version available at: www.bioassay.de