



PLA 3.0

Product Overview

Software for Biostatistical Analysis

// Supports all types of potency assays
// Covers the entire product and assay life cycle

Discover the Next Generation of Bioassay Analysis

All Assay Types Described in Ph. EUR and USP in One Software

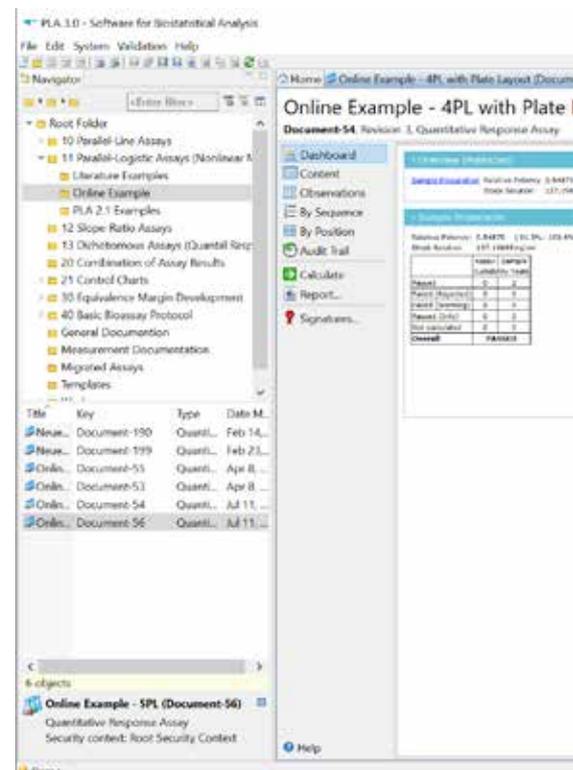
PLA 3.0 supports all types of biological assays according to European Pharmacopoeia, Chapter 5.3 and US Pharmacopoeia <111>, <1032>, <1033>, <1034>: Quantitative Response Assays (Parallel-Line, Parallel-Logistics, Slope-Ratio) and Dichotomous Assays (Quantal Response, Binary Assays). PLA 3.0 also supports all different weighting methods for combination calculations and the automatic data aggregation of independent assay data. Additional document types are available for Equivalence Margin Development, Control Charts and a Basic Bioassay Protocol.

Building an Assay Archive for Later Review

Over the months and years, you will spend considerable amounts of time and money on your assays. With PLA 3.0, you make sure that all your assays remain accessible for later review. PLA 3.0 keeps them in a database, ready to be retrieved with just a few clicks.

FDA Compliant, User- friendly Platform

Compliance with FDA 21 CFR Part 11 is one of the most important requirements for software meant for regulated environments. The challenge is to make the software fully compliant at the core and user-friendly on the surface. With PLA 3.0, we managed to achieve exactly that.



Covering the Entire Lifecycle of Your Product

With PLA 3.0, you can use the same software for the entire project - from development all the way through to production. The software will adapt to the stage of the project. We built several features into PLA 3.0 that make it not just suitable but in fact ideal for projects and teams of virtually any size.

Ready to Integrate With What You Already Use

PLA 3.0 is a highly versatile platform, ready to be extended to suit your particular needs. We developed a number of modules that allow you to connect PLA 3.0 to other programs or equipment, such as plate readers. In effect, your bioassay analysis will be independent of the device you are using to acquire the measurement values.

Users of PLA 2.0/2.1: Prepare to Reach the Next Level

When we published PLA 2.0 and 2.1, these programs were the most advanced we had developed so far. And it's the same with PLA 3.0. So it does make a lot of sense to switch from these previous versions to the newest one. You will reach the next level of bioassay analysis.

Going Beyond Service: Your PLA Support Contract

The PLA Support Contract helps you get the most out of PLA. The first year is included in every purchase. We provide a support portal for any issue around PLA and have a team of biostatisticians and (bio)chemists ready to support you.



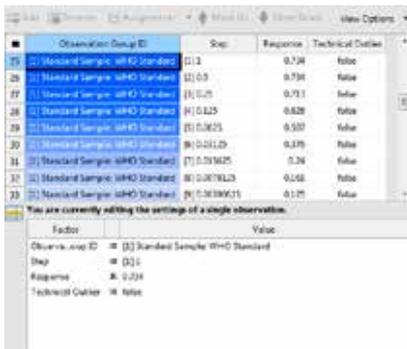
Continue reading to find out more about PLA 3.0 and its features.

PLA 3.0 UNDER THE HOOD

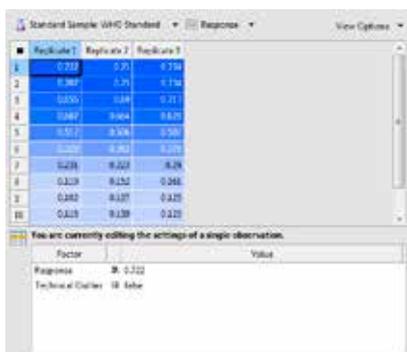
Intuitive basic concept: Handle data as documents

Easily extensible platform

Data Editor Perspectives:



Observation Setup ID	Step	Response	Technical Outlier
25	(1) Standard Sample: WHO Standard	0.734	False
26	(2) Standard Sample: WHO Standard	0.734	False
27	(3) Standard Sample: WHO Standard	0.731	False
28	(4) Standard Sample: WHO Standard	0.628	False
29	(5) Standard Sample: WHO Standard	0.537	False
30	(6) Standard Sample: WHO Standard	0.439	False
31	(7) Standard Sample: WHO Standard	0.26	False
32	(8) Standard Sample: WHO Standard	0.168	False
33	(9) Standard Sample: WHO Standard	0.175	False



Replicate 1	Replicate 2	Replicate 3
0.734	0.731	0.734
0.734	0.731	0.734
0.628	0.628	0.628
0.537	0.537	0.537
0.439	0.439	0.439
0.26	0.26	0.26
0.168	0.168	0.168
0.175	0.175	0.175



	1	2	3	4	5	6	7	8	9
A	4192	4642	4702	4702	4790	4743	4699	4699	4
B	4673	5059	5090	4970	4865	4657	4588	4588	4
C	4896	5305	5336	4763	5278	5388	5233	5	
D	4277	3283	3934	5890	6731	5895	7485	6	
E	5878	4233	3336	3395	3940	3379	3770	11	
F	2288	2100	2041	2069	2030	1971	2070	20	
G	2762	2762	2670	2669	2669	2643	2670	28	
H	2824	2725	424	430	494	2094	3473	22	

PLA 3.0 is a software platform for biostatistical analysis in GxP and non-GxP environments. The architecture of PLA 3.0 provides all the functionality required for regulated environments through the platform, while all statistical functionality is delivered by PLA Document Packages.

DOCUMENT CONCEPT

The basic idea is the concept of electronic documents, which we derived directly from the requirements of the FDA 21 CFR part 11 regulation. All data and meta data is kept in one single information unit - the document. The structure and capabilities of a document are defined in the document packages.

The platform protects these documents with electronic and digital signatures according to the 21 CFR part 11 regulation. To give you greater flexibility, documents are organized in folders where several restrictions can be applied (permissions, privileges, mandatory templates).

DOCUMENT PACKAGES

A document package contains one or more document types and calculation routines as well as required report templates and data for operational qualification (OQ).

The PLA 3.0 base system comes with

- Document Package for Biological Assays
- Document Package for Measurement Documentation
- Document Package for Generic Documents

You can install additional document packages into the platform. These document packages may be available for download or we will create them for you on demand.

Elastic Forms Editor

The Elastic Forms Editor is the central editor of PLA 3.0. It allows you to edit documents of any complexity in a fast, easy and efficient way. Context sensitive help for every field supports you with valuable information. The built-in template support lets you create and protect powerful templates to simplify usage and to support efficient standard operating procedures.

Data Editors

The system comes with three data editor perspectives. They allow different views on your data sets. You, as the user, can decide whether it is more efficient to view or edit data points line by line, or per sample along a dilution series or in a position factor perspective. Powerful tools like color-coding of fields help you to prevent input errors.

Reporting

Correct and validated reporting is critical in controlled environments. The PLA system supports validated reports to ensure a valid and trustable reporting of results.

BIOLOGICAL ASSAYS

PLA 3.0 supports all types of biological assays according to European Pharmacopoeia, Chapter 5.3 and US Pharmacopeia <111>, <1032>, <1033>, <1034>: Quantitative Response Assays (Parallel-Line, Parallel-Logistics, Slope-Ratio) and Dichotomous Assays (Quantal Response, Binary Assays). PLA 3.0 also supports all different weighting methods for combination calculations and the automatic data aggregation of independent assay data. Additional document types are available for Equivalence Margin Development, Control Charts and a Basic Bioassay Protocol.

PARALLEL-LINE ASSAY

A parallel-line assay is the classical method to calculate a relative potency for a dilution assay. It is a linear fit which covers only the (near-) linear portion of the dose-response relationship without their asymptotes.

PLA 3.0 supports parallel line assays along with additional functionality to determine acceptable regions of the dose-response curve (configuration optimization). The parallel-line method is a robust analytical method based on D.J. Finneys Statistical Methods in Biological Assay, 3. edition, 1978. It is supported by the European Pharmacopoeia and the US Pharmacopeia.

NONLINEAR QUANTITATIVE RESPONSE ASSAY

A nonlinear quantitative response assay (also known as a parallel-logistics assay) is a full curve fit method which takes the whole dose-response relationship into consideration, including asymptotes. PLA 3.0 supports different types of nonlinear full curve fits:

- 4-parameter logistic curve fit
- 5-parameter logistic curve fit
- 3-parameter logistic curve fit

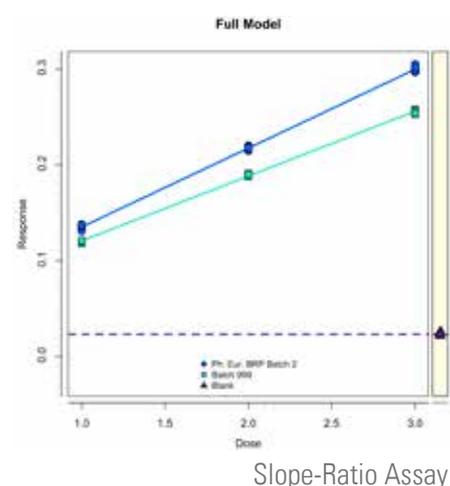
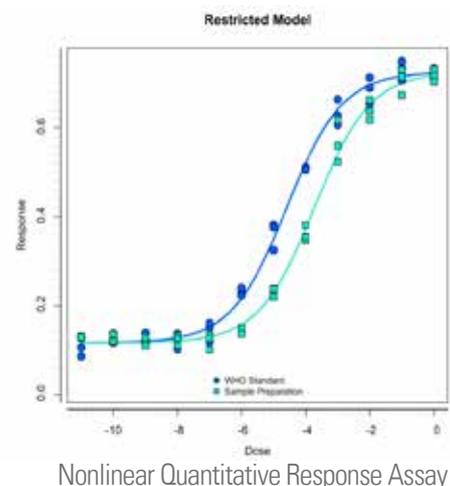
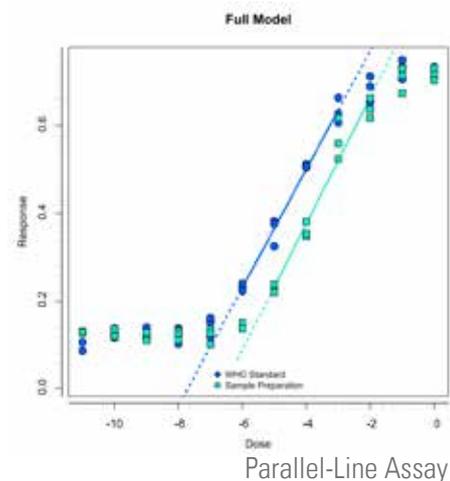
The 4-parameter logistic curve fit is the most common approach. It models a symmetric sigmoidal dose-response relationship. The 5-parameter logistic fit function adds an asymmetry parameter. The 3-parameter models is a reduced 4-parameter model, where one of the asymptotes has to be set to a fixed value or to the mean of a control line, which allows the system to deal with truncated data.

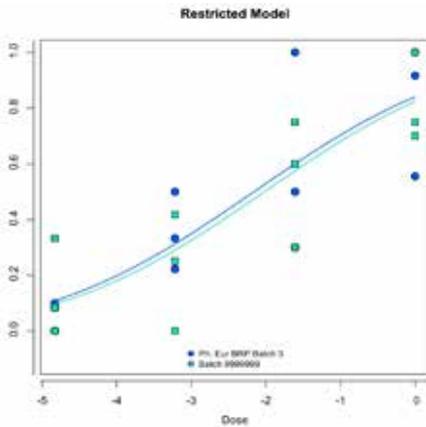
SLOPE-RATIO ASSAY

In contrast to parallel-line assays or nonlinear quantitative response assays, slope-ratio assays are carried out on a linear dose axis. They are most commonly used in microbiological applications.

The linear regressions of the standard and the sample intersect at zero dose. The potency is then calculated from the ratio of the slopes, the confidence intervals of the potencies are calculated using Fieller's Theorem.

PLA supports all assay types





Dichotomous Assay

Flexible assay setup allows virtually any assay configuration

DICHOTOMOUS ASSAY

Dichotomous Assays (which are also called quantal response assays or binary assays) are assays based on binary outcome, i.e. a number of specimens shows a given response at a specific dose of an active ingredient. The assays are usually analyzed using the probit- or logit-method. PLA 3.0 supports both of these functions.

STATISTICAL TOOLS

Flexible Assay setup

The assay setup in PLA 3.0 is very flexible. You can setup any assay system with a free number of test or control samples and control lines as well as free numbers of replicates and dilution steps. Symmetric and asymmetric assay setups are supported. When used in combination with the template system of PLA, any assay configuration can be set up in a GxP compliant way.

Outlier Detection

PLA 3.0 supports four optional outlier detection methods: Dixon Test, Grubb's Test, Studentized Residual and a test based on the standard deviation of the treatments.

Configuration Optimization

While the parallel-logistic assay (full curve fit) describes the whole dose-response correlation, parallel-line assays focus on the significant part of the dose-response relationship. PLA 3.0 is able to locate the significant parts of the dose-response correlation automatically to determine the optimal assay configuration.

Curve Fitting

In quantitative response assays both parallel-line assays and parallel-logistic assays (3-, 4- and 5-parameter sigmoidal functions) are implemented. Transformation functions for the response values are available for all models to reduce heteroscedasticity. The curve fitting of PLA 3.0 has been extensively optimized to provide high-quality curve fits, since bioassays tend to be very sensitive to the slightest deviations.

SOPHISTICATED TEST SYSTEM

Testing can be done either by difference/hypothesis testing, as described in the European Pharmacopoeia, or by similarity/equivalence testing, which was introduced by the US Pharmacopoeia chapters <111>, <1032>, <1033> and <1034>. The test system of PLA 3.0 is very flexible and lets you perform a number of different tests, which you can configure exactly according to your needs.

For example, PLA 3.0 can test for potency, both relative and absolute. In addition, you can define potency ranges and confidence intervals. You can even run a test based on the number of outliers.

COMBINATION OF ASSAY RESULTS

Combinations of assay results are not just means of potencies. To get optimal results, you need to consider the confidence intervals. PLA supports all methods of combination described by the European Pharmacopoeia and the US Pharmacopoeia. PLA also

supports all different weighting methods for combination calculations and automatic data aggregation of independent assay data.

BASIC BIOASSAY PROTOCOL

The Basic Bioassay Protocol is a powerful document type to implement the most common workflow in bioassay analysis: combining the results of multiple independent assay runs into reportable values.

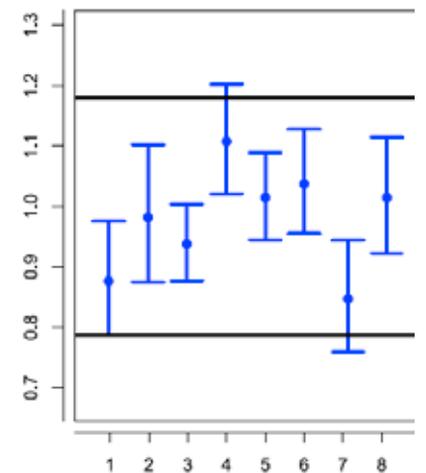
The Basic Bioassay Protocol controls all required steps: the assay is defined in the Basic Bioassay Protocol, which automatically creates a set of linked Quantitative Response Assays and Combination of Assay Results Documents. The results are automatically and safely transferred between the Quantitative Response Documents and the Combination Calculation – so no retyping is required.

Finally, the Basic Bioassay Protocol is capable of handling retests. Just raise the number of your assay replicates and the Basic Bioassay Protocol will add the required number of runs. This can be handled per assay run, but there is also an option to control this on a per sample level in multi sample assays.

EQUIVALENCE MARGIN DEVELOPMENT

The development of equivalence margins for use according to the US Pharmacopeia is a challenging task. PLA supports you with development assays which are used to develop the margins and verification assays that verify your test strategies. Test strategies are selections of available predefined or calculated margins that offer the possibility to include different strategies. The strategies can be visualized. The system is going to simulate a certain number of acceptable assays for every defined strategy to support the visual verification of the strategies. Besides this, the equivalence margin development offers a broad variety of equivalence tests.

At the end stands the development report that gives you many insights into the development process and results like for example detailed plots of the input assays.

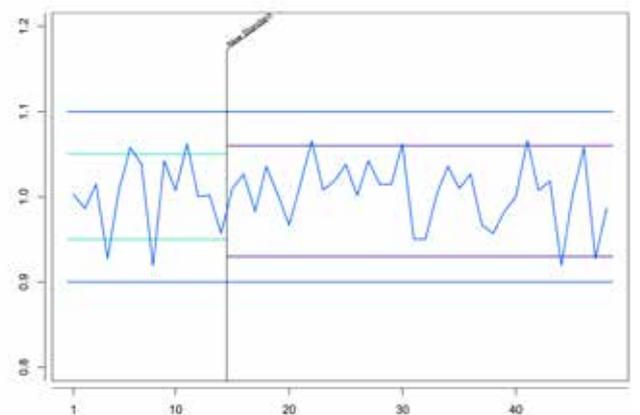


Visualization of Equivalence Margin Development

CONTROL CHARTS / MONITORING

The Control Chart document type in PLA 3.0 allows the trending of different parameters of your biological assay. Define any number of trending parameters and different limits to keep your assay under control.

You can use the Control Chart document in two ways. You can edit or import data from any source, allowing to use the trend chart universally. Or you can directly aggregate the corresponding data from your calculation results as required in regulated environments.



Control Chart

COVERING THE ENTIRE LIFECYCLE

PLA 3.0 covers the entire lifecycle -
from development to production

In order to use software in companies or teams of different sizes, it should be easily extensible and scaleable. We therefore built several features into PLA 3.0 that make it not just suitable but in fact ideal for projects and teams of virtually any size.

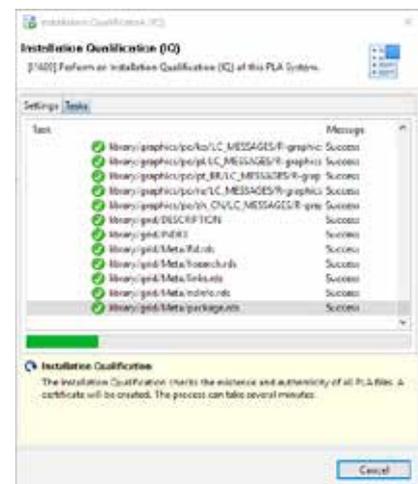
TEMPLATES

PLA 3.0 comes with a new template engine. Templates can be defined by authorized users. They decide about the visibility, access level and default values in a document. Templates can be signed electronically and the administrator can define the mandatory use of specific templates in the database or in database sections. The template engine was designed to support the easy implementation of standard operating procedures (SOPs) within PLA.

Easily scalable with templates

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 data to e.g. documentation systems and for the reporting into many target systems. Individual modules can be created at low cost.

Import Modules are now distinguished into Document Import Modules creating a complete document with all settings and Data Acquisition Modules. Data Acquisition Modules are able to import data into the data table of any document type. (Note: They replace the former PLA 2.x Import Modules.)

Document Import Modules

Document Import Modules generate fully specified documents of a specific type. They are useful when an external format contains every information required to create a specific document. E.g. if a third party program deals with biological assays a Document Import Module can be set up in a way where a completely specified quantitative response assay is delivered. In this case the Document Import Module converts all settings and creates the appropriate PLA 3.0 document.

Device-independent assay analysis -
use the reader system of your choice



Data Acquisition Modules

Data Acquisition Modules are used to connect external systems directly to the data tables of a PLA 3.0 document. Typical examples are Data Acquisition Modules for plate readers. A plate reader delivers a stream of measurement values that need to be imported to the data table of a specific document in a GLP/GMP compliant way. Data Acquisition Modules are the most common import modules used by PLA. Currently, we have many different Data Acquisition modules available.

Data Acquisition Modules are licensed by the supported external format. They are not specific to the target document type.

Document Export Modules

Export Modules are available to export PLA 3.0 Document to a specific External Format. They export the PLA 3.0 Document and transform them into the target format. They can be used to connect PLA to other external systems (e.g. LIMS systems).

TRANSFER OF DATA AND TEMPLATES

PLA allows to transfer data and templates between projects, sites and companies in a secure manner.

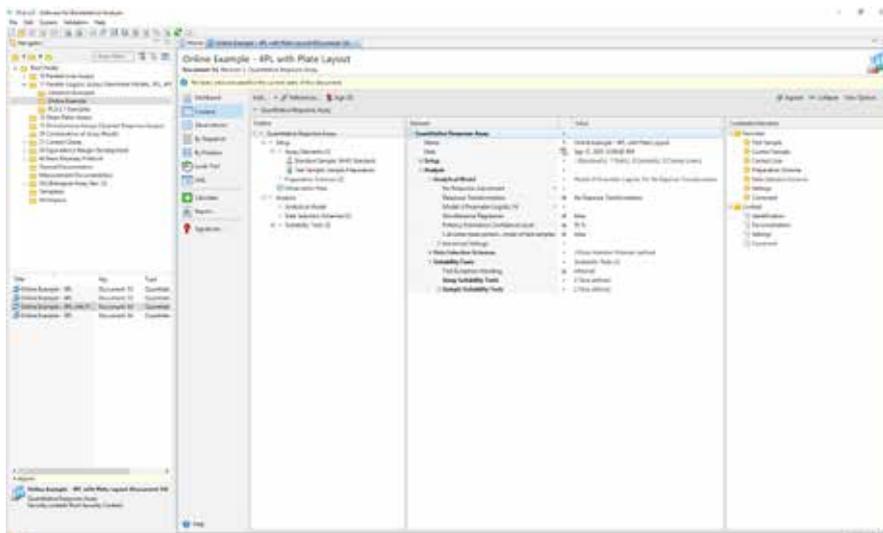
The trustability and integrity of the data is assured by a combination of electronic signatures, that are preserved in the transfer, and cryptographically secured data transfers. PLA secures the information with the help of its own integrated PKI (Public Key Infrastructure). This operation is completely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

ROLES AND PERMISSIONS

PLA 3.0 comes with an updated sophisticated permission system scalable from single seat to global installations. Typical roles are predefined in the system but can be altered to match your companies needs. All the settings are combined together in named security contexts that can easily be applied to new folders.

Your imported data remains fully traceable - all the time

Configure roles and permissions exactly the way you want them



Ideal framework for replacing legacy software

PLA 3.0 is fully FDA 21 CFR Part 11 compliant.

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 unauthorized access to the system.

ELECTRONIC SIGNATURES

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

DATA TRACEABILITY / AUDIT TRAIL

PLA has its own audit trail that covers all changes of data and properties of your documents and of all security features inside PLA. The audit trail can be inspected on a per-database and a per-document level. Filter and export functions have now been included into the base features of PLA 3.0. Acquired raw data can always be traced back to its original source.

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 3.0 FEATURE OVERVIEW

PLA 3.0 is an extensible software for bio-statistical analysis in GxP and non-GxP environments.

BIOLOGICAL ASSAY

Quantitative Response Assays/ Dichotomous Assays

- Analysis according to European Pharmacopoeia, Ch. 5.3 and US Pharmacopoeia <111>, <1032>, <1033>, <1034>
- Response Adjustment
- Response Transformations (linear, log, square, square root)
- Outlier Detection (4 models)
- Regression models
 - 3-, 4-, and 5-Parameter Logistic Fit
 - Linear regression
 - Probit-/Logit-Analysis
 - Simultaneous Regression
 - Slope Ratio
- Sophisticated Test System
 - Assay and Sample Suitability
 - Over 100 varieties of tests (F-Tests, Equivalence Tests, additional tests)
 - Conditional Tests
- Potency calculation with back calculation
- Configuration Optimization

Combination Of Assay Results

- Unweighted, weighted and semi-weighted
- Combination according to European Pharmacopoeia, US Pharmacopoeia <111> and <1034>
- Test system for combined potency
- Compliant aggregation from independent assays (optional)

Equivalence Margin Development

- Candidate calculation for up to 53 different equivalence margins
- Automatic aggregation of data from historic development assays
- Strategy verification - with verification

assays

- Comparison and visualization of different testing strategies
- Simulation of developed test system

CONTROL CHARTS

- Compliant aggregation of data from your assays (optional)
- Multiple control limits and limit tests

BASIC BIOASSAY PROTOCOL

- Easy workflow to calculate a reportable value for the potency from independent assay runs

MEASUREMENT DOCUMENTATION

Three different document types for the documentation of your measurement process: Equipment, Operator, Substance

PLATFORM

- Extensible Platform
 - Document Packages
 - Report Templates
 - Data Acquisition Modules
- Coexistence with PLA 2.0 and 2.1
- Microsoft Windows (tm) 7, 8, 10, 2008, 2012, 2016 supported.
- Supports authentication via LDAP/Active Directory

Data Organization

- Databases supported:
 - Microsoft SQL Server (tm)
 - File-based database
- Security
 - Role-based security model
 - Access authorization
- Audit Trail
 - Logs every document event
 - Logs every system event
- Electronic Signatures
 - Protect documents from modification
 - 21 CFR part 11 compliance

- Digital Signature
 - Protect data integrity

Document Handling

- 3 Data Editor Perspectives
 - By observation (by row)
 - By sequence (dilution sequence)
 - By position (e.g. plates)
- Report Engine
 - Validated reports
 - Extensible

GAMP Support

- Installation Qualification (IQ)
- Operational Qualification (OQ)
- Performance Qualification (PQ)
(Requires Validation Package)

PLA ADD-ONS

- PLA 3.0 Base System, including
 - Biological Assays
 - Measurement Documentation
 - Generic Document Types
- PLA 3.0 Data Acquisition Modules
- PLA 3.0 Document Import Modules
- PLA 3.0 Validation Package
- Customized Report Templates
- Individual Solutions

PLA SUPPORT CONTRACT

- 1 year of PLA Support Contract (maintenance contract) included with every purchase
- Priority support with a target response time of one business day and
- Access to 2nd level support (this includes scientific support)
- Upgrade and downgrade permission for all covered PLA products released during the maintenance time frame
- Notification service for relevant changes in the guidances
- Discounted training rates



For over 20 years, Stegmann Systems has been developing their software solution PLA which supports the development, execution and analysis of biological assays..

PLA is used by over 700 companies worldwide. Among them are the top 100 pharmaceutical and biotech companies together with laboratories, universities, research institutions and regulatory authorities.

The current version PLA 3.0 is fully compliant with GAMP, GMP, and 21 CFR Part 11 and follows the guidance from the USP and Ph. Eur. PLA is the most used software for biostatistical database solutions in highly regulated pharmaceutical and biotech industries.

PLA 3.0

- Supports all potency assay types:
 - US Pharmacopeia <111>, <1032>, <1033>, <1034>
 - European Pharmacopoeia, Chapter 5.3
- Covers entire product and assay life cycle
- Reuse your historic assay data
- Equivalence margin development
- Compliant assay monitoring
- Compliance with FDA 21 CFR Part 11

UPCOMING RELEASES

- PLA 3.0.5
 - New add-on management
 - Increased limits: PLA is now 64-bit
 - Improved data tables
- Dose-Response Analysis Package
 - Single curve analysis
 - Interpolation from a standard curve/calibration curve (ELISA)
 - Curve comparison (e.g. for assay optimization)
- Microbial Assays for Antibiotics Package
 - Determine the antimicrobial potency of antibiotics based on their anti-microbial activities according to US Pharmacopeia <81> and Japanese Pharmacopoeia



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