PLA 3.0

Release Notes

PLA 3.0.5 and Biological Assays Package 26

Release Notes PLA 3.0.5 (build 816)
Release Notes Biological Assay Package 26 SR1 (build 1043)
Release Notes Dose Response Analysis Package 1 (build 16)

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1 Welcome

Welcome to the Release Notes of PLA 3.0.5 (build 816), Biological Assay Package 26 (build 1043) and Dose Response Analysis Package 1 (build 16).

This document contains the cumulated Release Notes showing all new features, changes and fixes for all versions of PLA 3.0 since its initial release.

This document is primarily intended for Functional and System Administrators.

The release notes are structured into Release Notes for

- PLA Framework
- Biological Assay Package
- Dose Response Analysis Package

NOTES:

Before upgrading PLA, backup your PLA databases!

1. Updated document packages need to be activated in every database. If you do not actively update the document package in the package manager, PLA will still use the older mathematical routines.

2. PLA 3.0.5 requires a valid license. A support contract is required for updating your version. Every purchase within the last 12 months automatically has this support contract included. If you do not have a support contract contact our sales team at sales@bioassay.de.

3. PLA 3.0.5 does not contain any add-ons. They are downloaded or provided by file through the new add-on management which is located in the System menu.

4. PLA 3.0.5 requires a database schema upgrade to be performed. Open the Database Manager and press Repair for the database you want to open. PLA 3.0.4 or earlier will no longer be able to use this database after the schema upgrade. Run the Database Maintenance after the upgrade. It is necessary to assign the Database Maintenance privilege to the System Administrator Group to perform the maintenance.

5. PLA 3.0.5 requires new versions of the data acquisition modules. They are available in the add-on management. Separate distribution by Stegmann Systems is no longer required.

6. Document Structure upgrade might be required. After you upgraded your Biological Assay Package, you need to upgrade those documents you want to recalculate with the updated mathematical routines. We recommend upgrading the documents directly without creating new copies. For security reason the latter is the default in the upgrade process. If you make copies of your existing documents, please remember to upgrade the references if these documents are part of an aggregation. Note: PLA 3.0.5 does not introduce a new Biological Assay Package.

7. A database maintenance run is highly recommended, when you start using Biological Assay Package 24 or higher. The database maintenance run is required for supporting the updated Control Chart capabilities of Biological Assay Package 24 or higher. Please select Database Maintenance and then "Start a new maintenance with reinitialization of the list of document properties.". If you do not perform this maintenance run, Control Charts may contain only partial data.

8. Control Charts may require redefinitions if you are using Biological Assay Package 24 or higher. Please verify the correct behavior of your Control Charts.

9. Not all versions and revisions of the product have been released to the public. This document contains release notes for all public versions.

RELEASE NOTES HISTORY

Rev 1: Dec 10, 2020 Initial version.

2 Release Dates

	Version	Released
PLA Framework	3.0.0	22.05.2014
	3.0.2	12.11.2014
	3.0.3	27.02.2015
	3.0.4	20.05.2016
	3.0.4 SR1 (build 716)	01.09.2016
	3.0.4 SR2 (build 718)	21.12.2016
	3.0.4 SR3 (build 721)	07.04.2017
	3.0.4 SR4 (build 752)	14.05.2018
	3.0.4 SR5 (build 761)	03.09.2018
	3.0.4 SR6 (build 762)	28.09.2018
	3.0.5	10.12.2020
Biological Assay Package	14 included in PLA 3.0.0	22.05.2014
	17 included in PLA 3.0.2	12.11.2014
	18 included in PLA 3.0.3	27.02.2015
	19	18.03.2015
	20	13.07.2015
	21	10.11.2015
	22	23.12.2015
	23 included in PLA 3.0.4	20.05.2016
	24	05.05.2017
	25	15.01.2018
	25 SR1 (build 983)	09.02.2018
	25 SR2 (build 984)	22.02.2018
	25 SR3 (build 991)	13.04.2018
	25 SR4 (build 999)	03.08.2018
	25 SR5 (build 1015)	20.12.2018
	26	29.03.2019
	26 SR1 (build 1043)	17.05.2019
Dose Response Analysis Package	1	10.12.2020

Versions not listed here are internal versions and have never been released to the public.
The release notes document changes between the listed versions.

3 PLA 3.0.5 Release Notes

3.1 PLA Framework

The PLA 3.0.5 release is a milestone for PLA 3.0. It introduces five major aspects:

- **Dose-Response Analysis Package**. The Dose-Response Analysis Package is a major new package. It supports various additional biostatistical features for calibration curves, interpolation calculations, effective concentration calculation, spike-and-recovery analysis etc. This package is provided as part of the framework and does not require a purchase. It requires PLA 3.0.5 or higher.
- **Add-on Management**. The former package management has been replaced by a new add-on management. Add-ons are now provided in package files. A separate installation is no longer required. They are activated through the add-on management. The add-on management keeps track of your licenses and allows trial versions of add-ons you did not license. All former commercial off-the-shelf packages have been repackaged for the add-on management, which touches only the distribution. When you upgrade an existing database to PLA 3.0.5 the system will request migration of the components, which replaces them by the corresponding add-on distribution. If you have customer specific modules you need to request the corresponding packages to be migrated to the add-on system. This migration will be free of charge but please expect four to six weeks for delivery. These customer modules will also be provided through the add-on management. The catalog for the add-on management is provided as part of the new information packages.
- **Dashboard and Information Package**. The dashboard will now provide more news and insight into PLA 3.0. The dashboard makes use of the new information package. The information package replaces the Login News with a more detailed news system for the dashboard, the catalog for the add-on management and it provides the license keys for PLA and the add-ons which replaces the need for updating those keys manually. The information package may be provided manually, or it is downloaded automatically (default).
- **64 bit system**. PLA 3.0.5 is the first 64-bit version of PLA and replaces its Java Runtime Environment by OpenJDK. This allows PLA to make use of more than 1 GB of RAM for complex calculations. For memory management in terminal server environments (e.g. Citrix) the default memory allocation is still 512MB.
- **Updated handling of data tables**. The "Assignments" function has been replaced by "Adjust", which is a powerful replacement with updated capabilities e.g., to correct observation tables by sorting or adding of missing values. Consequently, it is no longer required to prepare the observation editor for the use of the sequence editor and position editor if the observation. You can directly start using the sequence editor or position editor, which is a huge improvement in the handling of data editors.

3.2 New

- PLA makes use of OpenJDK 64-bit. There is no longer a memory limit. Nevertheless, more memory needs to be request through the pla.properties file.
- Add-ons are the new distribution form of every package. Separate installations through setup programs are now longer supported. Add-ons can be downloaded automatically or you can get them as a single file from our website https://www.bioassay.de/
- Add-on licensing has been introduced allowing customers direct access to add-on through the add-on manager.
- Information packages are provided with news, customer-specific catalogs and license keys. They can be manually provided (download from https://www.bioassay.de/nc/informationpackage/ or they will be automatically downloaded by PLA during system startup. The Information Packages are stored locally and in the database.
- License Management keys has been replaced by the information packages.
- Add-on Management allows activation and deactivation of add-ons. A library of add-ons can be managed through add-on management. This library contains add-on that are available for database without download or separate distribution. Administrators may (but are not required to) manage these libraries which can be located on a central drive.

- Add-on trial versions can be requested through the add-on management.
- Add-on quote can be requested through the add-on management.
- Reason for change is now supported for copy, move, and delete operations.
- New placeholder for initial values: {Sequence:PADDING:PREFIX:SUFFIX} can be used for automatic numbering of runs. E.g. {Sequence:5:Assay_:_Method} leads to "Assay_00001_Method". Values created by the placeholder are always unique in the database.
- Creatable elements: right mouse button allows to add multiple instances at once.

3.3 Changed

- Configuration reports have been extended to support add-on management and information packages.
- Dashboard has been updated to included news and license specific news.
- User registration information is now stored in the %appdata% directory.
- Progress control for multiple documents is now managed in a single dialog.
- Delete operations make use of the progress dialog.
- The audit trail entries have been reworked for consistency and more details on system activities.
- If PLA is in trial mode, the repair function of the database management is deactivated to protect production databases.
- External hyperlinks in dashboards are now opened through the standard browser of the operating system.
- Document types in versions that are not licensed can now be opened in read-only mode.
- Privilege "Edit field protections" has been renamed to "Edit document with elevated privileges" for better clarity.
- Performance improvement of the audit trail viewer.
- Detail improvements of permission restrictions.
- The document dashboard is now reflecting the status of the document and no longer the saved document status allowing the dashboard to directly react on document changes.
- Translation feature in My account dialog has been corrected.
- Content editor and outline view: improvement of the right mouse button features.
- Observation data editor: Assignments have been replaced by "Adjust". Adjust adds huge flexibility in managing data tables. "Sort" allows to sort the table by position values or by group and sequence information. Reassign allows updating the observations group and sequence or position information. Add missing observations fills up all missing entries group and sequence or positions. Delete factor values clears either group and sequence or position data.
- Sequence editor displays the sequence values now consistently to the other editors without rounding.

3.4 Fixed

- Exception when deactivating LDAP certificates is now handled correctly.
- Handling LDAP certificates with deviations in the ServerName field has been improved.
- Certificate dialogs rearranged to make all fields fully visible.
- Configuration report: missing policy for immediate save of documents has been included.
- Configuration report: indirectly assign global permissions are now correctly displayed.
- Error messages in the data acquisition process have been updated.
- A problem with missing thread releases has been solved.
- The help view is now only visible in the content editor.
- Padding of keys for document templates has been corrected.
- False enablement for the folder properties dialog has been corrected.
- Reason for change for document templates is now being displayed correctly.
- Unexpected behavior of the database connection wizard when the target already existed has been corrected.
- Unexpected errors during report generation have not been detected as errors.
- A problem with operating system text size scaling above 175% has been fixed.
- Usage of Ctrl-S for save operations in the account management has been corrected.
- Inconsistent behavior of data acquisition when policy Change by import is set to 'denied' has been fixed.

- Content editor: editing of reference fields has been improved.
- Templates: use of placeholder {KeyedCounter} for initial values has been improved.
- Performance improvement for the color feature in all data editors.
- Database management: fixed a bug which prevented editing entries of removed databases.
- Document editor: improvement of copy&paste behavior.
- Fixed save behavior in the editor for permission restrictions of documents.
- Inconsistent behavior of using the Enter key in content and data editors has been fixed.
- Filter behavior of the sequence editor did not allow entries that were not yet present in the editor.
- Edit behavior of a third position factor in the position edit has been corrected.
- Edit behavior of datetime fields in the content editor has been corrected.
- Improved feedback when available memory is low.
- Fixed lock behavior for folders where the lock has been removed under some circumstances.
- Fixed lock behavior for documents when a copy process was not successful.
- Improved handling of template restriction for folders.
- False case sensitivity for profile names in data acquisition modules has been fixed.
- Various technical internal improvements and fixes.

3.5 PLA Data Acquisition Modules

PLA 3.0.5 requires updated versions of all data acquisition modules.

3.6 Known issues

- Back-migration to a former version of PLA 3.0 requires explicit deinstallation of PLA 3.0.5.
- Data acquisition modules should be run under administrative privileges for the first run.
- OpenLDAP is not officially supported in this version.

4 PLA 3.0.4 Release Notes

4.1 PLA Framework

Version: 3.0.4 SR6 (build 762) (Previous Version: PLA 3.0.3 (build 691)). PLA 3.0.4 includes Biological Assay Package Rev. 23.

Note: SR6 (build 762) is a new build of PLA 3.0.4. It is an updated build which fixes technical problems introduced with PLA 3.0.4. It does not modify capabilities of the system.

4.2 New

- PLA now supports authentication via LDAP (e.g. Windows Active Directory)
- New Login dialog to support native as well as directory based authentication.
- New Version of automation capabilities for running complex operations in the platform.
- Possibility to redirect the local configuration of PLA (pla.properties) to a central location
- Data format for the function "Open Externally" can be configured
- New database policy to control whether it is allowed to overwrite imported values by another import process
- "Change Document and Folder Key" is now a separate permission.
- New database policy controlling whether it is allowed to change document or folder keys.
- New database policy controlling whether a new document is saved before it is opened for editing. This enables better tracking of changes between a document and the template it is created from.
- Introduced a system account with name "_SYSTEM_". This account is used for signatures, automatically applied by the system. If there in an account with this name already existing in the database, it is disabled by the upgrade process.
- A feature for Database Maintenance and a corresponding permission "Database Maintenance". The permission needs to be assigned to a role after the upgrade process.! In new databases, it is assigned to the 'System Administrator Global Role'.
- SR5 (build 761) PLA is now distributed with a simplified installer for the PLA License System. The installer updates the license system drivers (haspdinst) and installs the PLA License Key Manager (RUS_MATRG) for easier handling of software license keys.

4.3 Changed

- Database schema has been updated from 3.01 to 3.04. Databases need to be upgraded to this scheme by pressing “Repair” in the database management dialog. Note: after the upgrade PLA 3.0.3 or earlier is no longer capable to connect to the database.
- An audit trail entry with action SCHEMA_UPDATE is written during the ‘repair’.
- Timestamps in audit trail entries in MS SQL databases are now written in UTC instead of the local time of the PLA client. Timestamps of the entries prior to the update to PLA 3.0.4 are not changed. UTC timestamps are used beginning with the SCHEMA_UPDATE audit trail entry for schema version 3.04.
- It is no longer possible to create an account with the name "_<Any Text>_". Those names are reserved for system use.
- The Package Management dialog shows only the installed version of a package or newer versions. The actions are renamed from 'install' to 'activate' and 'uninstall' to 'deactivate'.
- References in documents will work correctly after an export/import cycle of documents in document packages if all referenced documents are part of the imported document package.
- Document packages can only be imported completely.
- Import- and Data Acquisition Modules installed for an earlier version of PLA must be uninstalled prior the update. An updated version of the module must be installed after the update to PLA 3.0.4.
- Data Acquisition Modules now support a “Top and Clear” strategy, which removes all prior data values and starts the acquisition at the top row.
- Assignment of Security Contexts has been changed. Security Contexts are now assigned to all subfolders until another assignment is found.
- Improved initialization time during login. (about 50% speed improvement)

- SR2 (build 718): References to databases are realized via Database UUID (as seen in System - Database Policies – Advanced) instead of the Connection Profile UUID.
- SR3 (build 721): Database Maintenance has now an option to reinitialize the list of document properties to support Biological Assay Package 24.
- SR3 (build 721): CSV options are now available to the report engine.
- SR3 (build 721): Document properties without label are no longer reported with "Missing label".
- SR4 (build 752): Updated Runtime Installer for License Management to solve a performance issue with the installation under current versions of Microsoft Windows 10.

4.4 Fixed

- Observations cannot be moved up and down not when they are protected by a template.
- Font Sizing / Screen Resolution issues with Windows 10.
- Calculated values are now extracted into the digest during import.
- Configuration Report execution exceptions have been fixed.
- SR1 (build 716): Escaping of LDAP queries corrected (Username with comma)
- SR1 (build 716): System Lock with LDAP fixed.
- SR2 (build 718): Database Maintenance processes all documents and gives proper feedback for skipped documents.
- SR2 (build 718): The SSL Certificate used to connect to an LDAP server can be removed.
- SR3 (build 721): Performance update for automated processing of large data tables
- SR3 (build 721): Memory usage of the reporting engine has been optimized.
- SR4 (build 752): Modified usage of Windows handles to improve ressource usage.
- SR4 (build 752): Memory usage improvement by dynamic handling of HTML views
- SR4 (build 752): Improved Feedback during Data Acquisition
- SR4 (build 752): Fixed a problem preventing automatic update of data tables.
- SR5 (build 761): Fixed a problem with the display of mathematical formulas within the context help.
- SR5 (build 761): Fixed a focus problem within Date and Time cell editors within the document editor.
- SR5 (build 761): Fixed a problem with combining permissions from multiple document roles.
- SR5 (build 761): Fixed a lable problem within data acquisition modules not showing the effective settings for a certain import strategy.
- SR5 (build 761): Fixed a problem with the restriction of task permissions for Microsoft SQL Serverdatabases which made it impossible to active restriction for the Signature State.
- SR6 (build 762): Combining different restrictions over multiple permission assignments was not working as intended in some cases.
- SR6 (build 762): A performance problem when refreshing the display of audit trail entries in large databases has been solved.

4.5 PLA Data Acquisition Modules

Due to changes in the adapter of the framework and in the Biological Assay Package there are new versions of the import modules and data acquisition modules required.

5 PLA 3.0.3 Release Notes

5.1 PLA Framework

Version: 3.0.3 (build 691) (Previous Version: PLA 3.0.2 (build 677). PLA 3.0.3 includes Biological Assay Package Rev. 18.

5.2 New

- PLA notifies about outdated packages in a database. The notification can be disabled in the Database Policies
- A Configuration Report (aka Configuration Item List, CIL) summarizing the configuration of the database is now available. The Configuration Report is available from the System menu for users with 'Edit Database Policies' permission.
- New policy for the denial of document removal for signed documents. The removal of signed documents can now be restricted as a global policy.
- Permissions assignments can now be assigned by document mode (e.g. templates) and signature state (Document Roles).
- Templates can now be created directly from the New Document dialog.

5.3 Changed

- New Biological Assay Package version 18.
- Reason and Signature for one annotation can now be applied to all following annotations.
- The OQ and PQ dialogs have been improved to offer the same functionality as the IQ dialog.
- OQ/PQ now state DEVIATIONS DETECTED instead of FAILURE.
- The key F5 will now refresh references when it is used in documents that are in aggregation mode.
- Improved Audit Trail filter options.
- Permissions related to the Folder Properties dialog have been changed.
- The permission Read documents now allows to open the Folder Properties and view the contents of the General tab.
- The permission Edit documents now allows to edit the contents of the General tab of the Folder Properties dialog, excluding the Security Context of the folder.
- The permission Edit security contexts adds the permission to change the Security Context of the folder.
- The permission Read folder properties allows to view the contents of the Document Key Format and Document Restrictions tabs of the Folder Properties dialog.
- The permission Edit folder properties allows to edit the contents of the Document Key Format and Document Restrictions tabs of the Folder Properties dialog.
- The permission Create child objects has been renamed to Create new documents.
- PLA now installs and uses the HASP driver version 6.65.

5.4 Fixed

- Documents can now be created using document templates with an outdated document type version.
  - The document that will be created out of the template will be automatically upgraded to the newest document type version.
- Various text- and translation errors.
- Various performance and stability issues.
- PQ can now be executed using documents with an outdated document type version.
  - The documents will be automatically upgraded to the newest document type version, without changing the contents of the PQ package.
- OQ can no longer be executed using outdated OQ packages.
- The IQ can now be carried out without an existing database for better support of IT administrators.
- Users that have access to the Account Management can no longer open the Session Management if it is locked by another user.

- Password Expiry date is no longer miscalculated
- User preferences will now be saved correctly when PLA is exited using the login screen.
- User preferences will now be kept when PLA is updated to a newer version.
- Packages displayed in the Package Management are now sorted alphabetically.
- Users, Groups, Roles and Security Contexts displayed in the Account Management are now sorted alphabetically.
- The values of document reference elements within the Content View of the document editor can now be deleted.
- Document Keys can now be pasted into document reference elements within the Content View of the document editor.
- The status of a Database Connection Profile is now displayed correctly.

5.5 Known Issues

- When opening the Folder Properties of the *Root* folder in a database that has been created by a previous version of PLA, the Folder Properties dialog will incorrectly display *New Folder* as the current name of the *Root* folder. Workaround: The Folder Properties dialog will display the correct name of the Root folder once the Folder Properties were changed and saved using PLA 3.0.3.
- Upgrading the Biological Assays Package from version 17 to 18 in an existing database requires exclusive access to the database. Exclusive access to the database is not obtained automatically. It must be obtained by manually executing the appropriate function.
- Importing more than 500 documents from one previously exported document package may require adjustment of memory settings.

5.6 PLA Data Acquisition Modules

Due to changes in the adapter of the framework and in the Biological Assay Package there are new versions of the import modules and data acquisition modules required.

6 PLA 3.0.2 Release Notes

6.1 PLA Framework

Version: 3.0.2 (build 677) (Previous Version: PLA 3.0.0 (build 623). PLA 3.0.2 includes Biological Assay Package Rev. 17.

6.2 New

- Raw Data Traceability
- Source information for acquired raw data are recorded
- Protection of Technical Outlier states
- Protection of imported raw values
- Area related Electronic Signatures
  - Document Signature (whole document is signed and write protected)
  - Content Signature (the content editor values are signed. Data and Calculation Results are not protected)
  - Dataset Signature (the data values are signed)
- Find/Filter functionality for Generic Document Editor (CTRL + F)
- Automatic updating of aggregated data in the data table

6.3 Changed

- Improved license management
- Improved document differences in Audit Trail
- Improved multi-user handling (performance, stability)
- Improved performance while editing datasets
- Redesigned upgrading of document structures
- Added various system log-events to relieve customer support
- Updated to Biological Assay Package Version 17
- Updated to Measurement Documentation Package Version 4

6.4 Fixed

- Various text- and translation-errors have been corrected
- Various performance and stability issues
- Error that could result in failed Operational Qualification due to strict calculation timeout
- Error prohibiting the OQ Certificate from print
- Updated Sentinel LDK (license system) driver
- Error that could block the creating of new documents for users with highly restricted permissions when using the favorites feature

6.5 Known Issues

- The date when a password expires is miscalculated in the current version. The password remains valid for one day longer than configured.
  - Workaround: Configure password expiry one day shorter than the expiry should be.

6.6 Document Package: Measurement Documentation

Version: 4 (Previous Version: 3)

6.7 Document Type: Substance

6.8 Changed

- Added additional properties for the detailed documentation of a substance.

6.9 PLA Data Acquisition Modules

Due to changes in the adapter of the framework and in the Biological Assay Package there are new versions of the import modules required.

7 PLA 3.0.0 / PLA 3.0.1 Release Notes

PLA 3.0.0 (build 623) was the initial release of PLA 3.0. PLA 3.0.0 includes Biological Assay Package Rev. 14.

PLA 3.0.1 was never released to the public.

8 Release Notes

8.1 Integration Report Package 1.3.0 (Build 25)

8.1.1 New

- Reporting of data acquisition information.
- Support of version 26 of the Biological Assay Package.

8.2 INTEGRATION REPORT PACKAGE 1.2.0 (BUILD 16)

8.2.1 NEW

- Support of version 25 of the Biological Assay Package.

8.2.2 CHANGED

- Names, especially test and parameter names, have been adapted to the names of version 25 of the Biological Assay Package.

8.3 INTEGRATION REPORT PACKAGE 1.1.0 (BUILD 15)

8.3.1 NEW

- Support of version 24 of the Biological Assay Package.

8.4 INTEGRATION REPORT PACKAGE 1.0.0 (BUILD 12)

8.4.1 CHANGED

- The meta information block including the document key has been added to the integration reports for the Quantitative Response Assay.

8.4.2 FIXED

- Resolved an issue, that the analytical model name has not been reported.

8.5 INTEGRATION REPORT PACKAGE 1 (BUILD 10)

8.5.1 NEW

- Initial release of the Integration Report Package.

Biological Package 26 Release Notes

8.6 Document Package: Biological Assays

Version: 26 (Build 1043) (Previous Version: 25).

8.7 New

8.7.1 Combination of Assay Results

- Combination Calculations according to USP <111> Method 2 are now supported.
- Better control of potency combination calculation type (relative, absolute or both).
- A plot has been added to visualize the combination calculation result.

8.7.2 Equivalence Margin Development

- Added equivalence margin development support for
  - Test: Sum-of-squared non-linearity to sum-of-squares regression
  - Test: Normalized difference of asymptotes

8.7.3 Quantitative Response Assay

- New suitability tests:
  - Test: Sum-of-squared non-linearity to sum-of-squares regression
  - Test: Normalized difference of asymptotes
  - Test: Log potency range
- Selection of a specific control line has been added for all suitability tests supporting the scope control line.

8.7.4 Test System Definition Document (Quantitative Response Assay)

- New suitability tests:
  - Test: Sum-of-squared non-linearity to sum-of-squares regression
  - Test: Normalized difference of asymptotes
  - Test: Log potency range

8.8 Changed

8.8.1 Help Texts Revision

- The help texts for the document types of the biological assay package have been completely revised.

8.8.2 Combination of Assay Results

- If no suitability tests are defined the overall test status is displayed as “Passed (no tests available)”.

8.8.3 Control Chart

- Defined plots are displayed as empty plots when no data is available.

8.8.4 Dichotomous Assay

- The test names of the "Additional Tests: ..." have been changed to "Test: ..."

8.8.5 Quantitative Response Assay

- Configuration of the element “Update mode” for the substance reference has been enabled.

- The comparison operations for evaluation suitability tests with activated rounding have been replaced by a more robust relative comparison approach.
- Standardization of the handling of percentage-based suitability tests. For all percentage-based tests, margins are entered as percentage values und results are given as percentage values.
- Performance of the range optimizer has been improved by omitting unneeded configurations.

8.9 Fixed

8.9.1 Basic Bioassay Protocol

- New comment text elements are now empty.
- SR1 (build 1043) Labels for combination methods in document, dashboard and report harmonized.
- SR1 (build 1043) Display of the unit for absolute potency and the corresponding confidence level has been harmonized and missing units have been added.

8.9.2 Combination of Assay Results

- A percentage sign has been added in the report for the value element of the "Test on Mean of CV (%)".
- SR1 (build 1043) Resolved an issue where the results for some combination calculation methods was not transferred to the Basic Bioassay Protocol.
- SR1 (build 1043) Labels for combination methods in document, dashboard and report harmonized.

8.9.3 Control Charts

- The refresh operation of the control chart terminated with an unexpected error when specific special characters have been used as chart labels.

8.9.4 Equivalence Margin Development

- The order of suitability test output in the margin development overview table has been corrected.
- The warning for violation of independence has only been displayed for at least 3 samples.
- SR1 (build 1043) Label for the coefficient of variation in tables have been corrected to CV.
- SR1 (build 1043) Resolved an issue where in the German version label and description for "Export tests" were interchanged.
- SR1 (build 1043) Fixed an issue where the scope for the "Test: Sum of Squares Non-Linearity" was set incorrectly by the "Export tests" task.

8.9.5 Quantitative Response Assay

- Fixed a problem where numerical inaccuracies caused by floating-point number representations in combination with activated rounding could lead to seemingly false decisions when the rounded test result was identical to the rounded margin. This has been fixed by the introduction of a robust comparison approach (epsilon test).
- "Test: Sum of Squares Regression" offered a selection for extent. This has been removed.
- Resolved an issue where F-Tests reported an incorrect p-value if rounding was activated.
- Resolved an issue where warning messages containing quotation marks have been displayed incorrectly.
- Fixed a problem where range optimization was automatically deactivated if one sample has activated optimization by using full range and another sample has deactivated the optimization process.
- Resolved an issue where the "Test: Potency Confidence Interval (%)" has not been calculated, if it is defined as a one-sided test with only a lower margin.
- Resolved an issue where the test status of the "F-Test (Hypothesis Test) – Significance of Square Coefficient" can be incorrect if the test is performed based on the p-value without using rounding.
- SR1 (build 1043) Resolved an issue where the calculation has been aborted without result, if the denominator during evaluation of the F-Test (Significance Test) Significance of Non-Parallelism is zero.

- SR1 (build 1043) Resolved an issue of a faulty test decision for tests with activated rounding, if the tested value was very close to the test boundary.
- SR1 (build 1043) Resolved an issue where the "Test: Normalized difference of asymptotes" is not calculated for some inputs.
- SR1 (build 1043) Resolved some minor reporting and graphic issues.

8.9.6 Quantitative Response Assay

- SR1 (build 1043) Suitability test labels in report and dashboard harmonized.

9 Biological assay Package 25 Release Notes

9.1 Document Package: Biological Assays

Version: 25 (Build 1015) (Previous Version: 24).

9.2 Preface

SR5 (build 1015) is a new build of Biological Assay Package 25. It is an updated build which fixes a few technical problems identified after the release of Biological Assay Package 25. It does not modify capabilities of the system. If you already have previously installed a former Biological Assay Package 25 it is recommended to reinstall the Service Release Package (build 1015) on all computers where you have installed previous builds and to reactivate the package within the package manager in all databases.

9.3 New

9.3.1 Basic Bioassay Protocol

- When generating Quantitative Response Assay documents, the generate task adds a link to the generating Basic Bioassay Protocol document into the generated Quantitative Response Assay document in the comment section.

9.3.2 Control Charts

- Markers are available in the Control Chart graphics.
- Control Chart graphic now also contains a box-and-whisker plot of the Input data.
- The report now contains an input data table.
- Improved display handling of plots with very small or very large numbers of observations.
- New XML-Excel report format.
- Document title of the referenced documents has been added to the dataset.
- The control charts now support single line text columns.

9.3.3 Equivalence Margin Development

The Equivalence Margin Development has been completely reworked.

- The Equivalence Margin Document supports Development and Verification Assays. Development Assays are used to develop the margins. Verification Assays can be used to verify test strategies.
- Test Strategies are selections of available predefined or calculated margins. Different strategies can be included.
- Strategy Visualization is available. The system simulates a certain number of acceptable assays for every defined strategy to support the visual verification of the strategies.
- New tests available:
  - Equivalence Test - Difference of Parameter Estimates: C Parameter (Nonlinear Models)
  - Equivalence Test - Difference of Parameter Estimates: Slope (Linear Models) for Slope Ratio Models
  - Equivalence Test - Difference of Parameter Estimates: Intercept (Linear Models) for the Parallel Linear Line Model
  - Equivalence Test - Ratio of Parameter Estimates: C Parameter (Nonlinear Models)
  - Equivalence Test - Ratio of Parameter Estimates: Slope (Linear Models) for Slope Ratio Models
  - Equivalence Test - Ratio of Parameter Estimates: Intercept (Linear Models) for the Parallel Linear Line Model
  - Equivalence Test - Scaled Parameter Range: C Parameter (Nonlinear Models)
  - Equivalence Test - Scaled Parameter Range: Slope (Linear Models) for Slope Ratio Models
  - Equivalence Test - Scaled Parameter Range: Intercept (Linear Models) for the Parallel Linear Line Model
  - Point Estimate Tests - Parameter Estimate

  - Point Estimate Tests - Difference of Parameter Estimates
  - Point Estimate Tests - Ratio of Parameter Estimates
  - Test - Sum of Squares Regression
  - Test - Sum of Squares Non-Linearity - Assay Element
  - Test - Residual Error
  - Test - Pure Error
- Development of asymmetric margins is supported and the default setting.
- The development report has been completely reworked to reveal much more insight into the development process and results.
- Detailed plots of the input assays have been added to the equivalence margin development report.
- A verification section has been added to the equivalence margin development report.
- A visualization section has been added to the equivalence margin development report.
- Full automated export of developed test systems as Test System Definition Documents is supported.
- Comparison of different test strategies is supported.
- SR3 (build 991) Multiple 'Term' elements are supported for the property filter of 'Column: Section'.

9.3.4 Quantitative Response Assay

- New suitability tests:
  - Equivalence Test - Difference of Parameter Estimates: C Parameter (Nonlinear Models)
  - Equivalence Test - Difference of Parameter Estimates: Slope (Linear Models) for Slope Ratio Models
  - Equivalence Test - Difference of Parameter Estimates: Intercept (Linear Models) for the Parallel Linear Line Model
  - Equivalence Test - Ratio of Parameter Estimates: C Parameter (Nonlinear Models)
  - Equivalence Test - Ratio of Parameter Estimates: Slope (Linear Models) for Slope Ratio Models
  - Equivalence Test - Ratio of Parameter Estimates: Intercept (Linear Models) for the Parallel Linear Line Model
  - Equivalence Test - Scaled Parameter Range: C Parameter (Nonlinear Models)
  - Equivalence Test - Scaled Parameter Range: Slope (Linear Models) for Slope Ratio Models
  - Equivalence Test - Scaled Parameter Range: Intercept (Linear Models) for the Parallel Linear Line Model
  - Point Estimate Tests - Parameter Estimate for all parameters including Slope (Nonlinear Models)
  - Point Estimate Tests - Difference of Parameter Estimates for all parameters
  - Point Estimate Tests - Ratio of Parameter Estimates for all parameters
  - Test - Sum of Squares Regression
  - Test - Sum of Squares Non-Linearity - Assay Element
  - Test - Residual Error
  - Test - Pure Error
  - Test - Relative LOF error (%)
- Test System Definition Document (Quantitative Response Assay) can be referenced in the Quantitative Response Assay. The test definitions of the Test System Definition Document (Quantitative Response Assay) will be evaluated, when evaluating this Quantitative Response Assay.
- New report: Detailed Report with compact test output.
- The calculation result now provides the 'Lambda'-value of linear models for reporting in custom reports.
- Upper and lower margins in suitability test are now optional. This enables the possibility of defining one sided tests.
- The order of the test definition in the document content controls the order of the test results in the report.
- The assay element specific versions of 'Test: Minimal R^2' and 'Test: Sum of Squares Non-Linearity' can now be defined by using the 'Extent' element in the test definition.
- The structure and ordering of the test definitions in the document has been reworked.

9.3.5 Reports

- Mark down syntax is supported in reporting of comment elements.

9.3.6 Test System Definition Document (Quantitative Response Assay)

- New document type for holding test systems for Quantitative Response Assay document types. Quantitative Response may link this document type as an additional (and optional) way to deal with test systems.
- Report for the Test System Definition Document (Quantitative Response Assay).

9.4 Changed

9.4.1 Combination of Assay Results

- The element 'date' has been added to the document structure.

9.4.2 Quantitative Response Assay

- Default label for the response column in the dataset is now "Response".
- Improved evaluation strategy for range optimization with 'Maximum Range', such that the calculation has a much better performance, if a passed configuration exists.
- Improved error handling for the Grubbs outlier detection method.
- The document outline now also contains the defined suitability tests.
- The word 'Additional' in the labels of 'Additional Test: ...' has been removed
- Harmonization of parameter names:

Parameter Name Bioassay Package 25	Parameter Names in Earlier Versions
A Upper Asymptote (Nonlinear Models)	Upper Asymptote (A)
B Parameter (Nonlinear Models)	Slope (B)
C Parameter (Nonlinear Models)	Inflection Point (C)
D Lower Asymptote (Nonlinear Models)	Lower Asymptote (D)
G Asymmetry Parameter (Nonlinear Models)	Asymmetry Parameter (G)
Intercept (Linear Models)	Intercept
Slope (Linear Models)	Slope

- SR1 (build 983) The range optimizer performance has been improved for identical range with one test/control sample.
- SR1 (build 983) The range optimizer performance has been improved for identical treatment number with one test/control sample.
- SR3 (build 991) The labels for the 3 parameter models have been replaced by non-camel case labels.
- SR3 (build 991) An error message is given, if for strict test exception handling the full or the restricted regression model fit cannot be calculated. In this case the overall status of the corresponding assay is set to ‘Failed (Warning)’.
- SR4 (build 999) Introduced relative comparisons with 12 significant digits for the evaluation of equivalence tests.

9.5 Fixed

9.5.1 Basic Bioassay Protocol

- SR1 (build 983) Resolved a problem, that Quantitative Response Assays have been generated with an invalid date/time element in the documentation section.
- SR5 (build 1015) Resolved an issue, that generated Combination of Assay Results documents generated based on a template containing a date element are incorrectly constructed.

- SR5 (build 1015) Resolved an issue, that generated Quantitative Response Assay documents generated based on a template containing a substance information element are incorrectly constructed.

9.5.2 Combination of Assay Results

- The combination calculation for Dichotomous Assays supports potency units.
- SR1 (build 983) Resolved a problem where the status 'no tests applied' has been falsely reported.
- SR4 (build 999) Resolved a problem with the report generation if substance identification was set.
- SR4 (build 999) Label change for homogeneity tests which cannot be calculated.

9.5.3 Control Charts

- Resolved a problem, that charts without control limits could not be calculated.

9.5.4 Dichotomous Assay

- Resolved an issue where the calculation terminated with an error, if absolute potency defined by stock solution, absolute potency defined by raw material in combination with dilution factors has been used.
- Reports: The page break behavior of the potency table has been corrected.

9.5.5 Equivalence Margin Development

- SR2 (build 984) Resolved an issue that the definition range of the plot has been chosen too narrowly, if the referenced assays used decimal logarithm or natural logarithm.
- SR2 (build 984) Resolved an issue, where values of a defined sequence in scientific notation were not shown in the report.
- SR3 (build 991) Resolved an issue, where the Generate routine for test system documents did not transfer the confidence level settings into the target documents.
- SR4 (build 999) Resolved an issue, that sometimes the confidence level has not been transferred correctly to generated test system documents.
- SR4 (build 999) The ordering of the tests in the verification table has been corrected.

9.5.6 Quantitative Response Assay

- Resolved an issue, where an obsolete version of the psf-Import has been used, after activation of the Biological Assay Package 24 in an existing PLA database.
- Resolved an issue in the recursive behavior of the Dixon test leading to a removal of too many data points, when the values of the data points were equal.
- The confidence level of an equivalence test is now displayed as percentage value and the compact report also contains this value.
- The reporting of the margins for the Test: Relative Potency Range (%) has been corrected.
- Resolved a problem, where the calculation terminated with an unknown exception, if the value of a user variable contained some special combinations of backslashes (\) followed by another character.
- Resolved an issue, where the range optimizer calculation could not be executed, when too many technical outliers had been removed.
- Resolved an issue with line breaks in the test result output in the report.
- SR1 (build 983) Resolved a problem which interrupted the calculation unexpectedly when the range optimizer has been used with maximum range in combination with simultaneous regression in assays with multiple test/control samples.
- SR1 (build 983) Resolved a problem which interrupted the calculation unexpectedly when the range optimizer has been used with maximum range in combination identical range or identical treatment numbers in assays with at least one control sample.
- SR3 (build 991) Resolved a problem, where some of the suitability tests could not be evaluated as one sided tests.
- SR3 (build 991) Resolved a problem, where the studentized residual test did not detect correct values if used in combination with range partial.

- SR3 (build 991) Resolved an issue, where the compact report of suitability test results did not contain the severity level for tests with severity ‘Reject’.
- SR4 (build 999) The elements ‘Severity’ and ‘Scope’ for suitability tests are mandatory.
- SR5 (build 1015) Resolved an issue in the calculation of the (Externally) Studentized Residuals outlier detection method.

9.5.7 Reports

- Resolved a rounding issue on the report level, where numbers with a certain structure are rounded down instead of up.

9.5.8 Test System Definition Document (Quantitative Response Assay)

- SR4 (build 999) The elements ‘Severity’ and ‘Scope’ for suitability tests are mandatory.

10 Biological assay Package 24 Release Notes

10.1 Document Package: Biological Assays

Version: 24 (Build 904) (Previous Version: 23).

10.2 Preface

With Biological Assay Package 24 Control Charts have been reworked. The list of available properties for charting has received updates.

- Additional Properties are available for Charting
- The labels have been changed to clarify the purpose of the property

IF YOU ACTIVATE BIOLOGICAL ASSAY PACKAGE 24 WITHIN A DATABASE A DATABASE MAINTENANCE RUN NEEDS TO BE PERFORMED WITH THE OPTION "START A NEW MAINTENANCE WITH REINITIALIZATION OF THE LIST OF DOCUMENT PROPERTIES.". THIS WILL UPDATE THE INTERNAL REGISTRY OF PLA'S DOCUMENT PROPERTIES. IF YOU DO NOT PERFORM THIS STEP THE REGISTRY MAY BE INCOMPLETE. BIOLOGICAL ASSAY PACKAGE 24 WILL EXTRACT THE PROPERTIES ALSO FOR OLDER DOCUMENTS.

CONTROL CHART WITHIN YOUR DATABASE NEED TO BE UPDATED AFTER THIS. YOU NEED TO VERIFY THAT THE PROPERTY KEYS FOR THE CHARTED VALUES ARE STILL FUNCTIONAL OF WHETHER YOU NEED TO RESELECT THEM (SEE TABLE BELOW).

10.3 New

10.3.1 Quantitative Response Assay

- EC50 value is provided for control charts.
- Entries of the ANOVA table are now provided for control charting.
- Optional Response Value Upper and Lower Limits. Values above or below these limits are masked as technical outliers during the calculation.
- The impact of Not Calculated Tests on the assay result can be specified now.
- PSF import now supports PLA 2.0 Builds 546 and 547.

10.4 Changed

10.4.1 Quantitative Response Assay

- Report: Label 'Equidistant Sequence' is changed to 'Linear Sequence'
- For comparability of the results PSF import defines a Response Value Lower Limit of 0 for PLA 2.0 imports with non-linear regression models (4- and 5-parameter fit). PLA 2.1 imports have not been changed.

10.4.2 Data Aggregation

- Labels for aggregation of data values (document properties) have been completely revised.
- The following property keys have been changed for consistency. If your Control Charts make use of one of these, it requires an update.

Old Property key	New Property Key
http://stegmannsystems.com/bioassay/date	http://www.stegmannsystems.com/bioassay/date
http://stegmannsystems.com/bioassay/status	http://www.stegmannsystems.com/bioassay/status

http://stegmannsystems.com/bioassay/ControlLineMinimum	http://stegmannsystems.com/edp/document/property/qra/controlline_min
http://stegmannsystems.com/bioassay/ControlLineMaximum	http://stegmannsystems.com/edp/document/property/qra/controlline_max
http://stegmannsystems.com/bioassay/ControlLineMean	http://stegmannsystems.com/edp/document/property/qra/controlline_mean
http://stegmannsystems.com/bioassay/ControlLineStandardError	http://stegmannsystems.com/edp/document/property/qra/controlline_stderr
http://stegmannsystems.com/bioassay/ControlLineCoefficientOfVariation	http://stegmannsystems.com/edp/document/property/qra/controlline_cov
http://stegmannsystems.com/bioassay/RestrictedRegressionParameterAMinusD	http://stegmannsystems.com/edp/document/property/qra/fold_difference_restricted
http://stegmannsystems.com/bioassay/RestrictedRegressionParameterADividedByD	http://stegmannsystems.com/edp/document/property/qra/fold_ratio_restricted
http://stegmannsystems.com/bioassay/RestrictedRegressionParameterA	http://stegmannsystems.com/edp/document/property/qra/a_restricted
http://stegmannsystems.com/bioassay/RestrictedRegressionParameterB	http://stegmannsystems.com/edp/document/property/qra/b_restricted
http://stegmannsystems.com/bioassay/RestrictedRegressionParameterCTestControl	http://stegmannsystems.com/edp/document/property/qra/c_restricted
http://stegmannsystems.com/bioassay/RestrictedRegressionParameterCAntilogTestControl	http://stegmannsystems.com/edp/document/property/qra/c_antilog_restricted
http://stegmannsystems.com/bioassay/RestrictedRegressionParameterCStandard	http://stegmannsystems.com/edp/document/property/qra/c_restricted_std
http://stegmannsystems.com/bioassay/RestrictedRegressionParameterCAntilogStandard	http://stegmannsystems.com/edp/document/property/qra/c_antilog_restricted_std
http://stegmannsystems.com/bioassay/RestrictedRegressionParameterD	http://stegmannsystems.com/edp/document/property/qra/d_restricted
http://stegmannsystems.com/bioassay/RestrictedRegressionParameterG	http://stegmannsystems.com/edp/document/property/qra/g_restricted
http://stegmannsystems.com/bioassay/RestrictedRegressionParameterR	http://stegmannsystems.com/edp/document/property/qra/r_restricted
http://stegmannsystems.com/bioassay/RestrictedRegressionIntercept	http://stegmannsystems.com/edp/document/property/qra/intercept_restricted
http://stegmannsystems.com/bioassay/RestrictedRegressionSlope	http://stegmannsystems.com/edp/document/property/qra/slope_restricted
http://stegmannsystems.com/bioassay/UnrestrictedRegressionParameterAMinusD	http://stegmannsystems.com/edp/document/property/qra/fold_difference_unrestricted
http://stegmannsystems.com/bioassay/UnrestrictedRegressionParameterADividedByD	http://stegmannsystems.com/edp/document/property/qra/fold_ratio_unrestricted
http://stegmannsystems.com/bioassay/UnrestrictedRegressionParameterA	http://stegmannsystems.com/edp/document/property/qra/a_unrestricted
http://stegmannsystems.com/bioassay/UnrestrictedRegressionParameterB	http://stegmannsystems.com/edp/document/property/qra/b_unrestricted
http://stegmannsystems.com/bioassay/UnrestrictedRegressionParameterC	http://stegmannsystems.com/edp/document/property/qra/c_unrestricted

http://stegmannsystems.com/bioassay/UnrestrictedRegressionParameterCAntilog	http://stegmannsystems.com/edp/document/property/qra/c_antilog_unrestricted
http://stegmannsystems.com/bioassay/UnrestrictedRegressionParameterD	http://stegmannsystems.com/edp/document/property/qra/d_unrestricted
http://stegmannsystems.com/bioassay/UnrestrictedRegressionParameterG	http://stegmannsystems.com/edp/document/property/qra/g_unrestricted
http://stegmannsystems.com/bioassay/UnrestrictedRegressionIntercept	http://stegmannsystems.com/edp/document/property/qra/intercept_unrestricted
http://stegmannsystems.com/bioassay/UnrestrictedRegressionSlope	http://stegmannsystems.com/edp/document/property/qra/slope_unrestricted
http://stegmannsystems.com/bioassay/UnrestrictedRegressionAbsoluteEc50TestControl	http://stegmannsystems.com/edp/document/property/qra/absolute_ec50_tst_unrestricted
http://stegmannsystems.com/bioassay/UnrestrictedRegressionAbsoluteEc50Standard	http://stegmannsystems.com/edp/document/property/qra/absolute_ec50_std_unrestricted
http://stegmannsystems.com/bioassay/UnrestrictedRegressionEc50	http://stegmannsystems.com/edp/document/property/qra/ec50_unrestricted
http://stegmannsystems.com/bioassay/ControlLineMinimum	http://stegmannsystems.com/edp/document/property/qra/controlline_min
http://stegmannsystems.com/bioassay/ControlLineMaximum	http://stegmannsystems.com/edp/document/property/qra/controlline_max
http://stegmannsystems.com/bioassay/ControlLineMean	http://stegmannsystems.com/edp/document/property/qra/controlline_mean
http://stegmannsystems.com/bioassay/ControlLineStandardError	http://stegmannsystems.com/edp/document/property/qra/controlline_stderr
http://stegmannsystems.com/bioassay/ControlLineCoefficientOfVariation	http://stegmannsystems.com/edp/document/property/qra/controlline_cov
http://stegmannsystems.com/bioassay/RestrictedRegressionParameterAMinusD	http://stegmannsystems.com/edp/document/property/qra/fold_difference_restricted

10.5 Fixed

10.5.1 Quantitative Response Assay

- PSF-Import: The suitability test Ratio of Dynamic Ranges will be imported now.
- PSF-Import: Equivalence Test EC50 will be neglected.
- PSF-Import: Import of Additional Test: Maximal Number of Outliers has been fixed.
- PSF-Import: The ANOVA model in case of split assay is now determined by the current preparation.
- PSF-Import: Allocation o the dose values to the assay elements has been corrected.
- Report: Fixed a number formatting issue for the Additional Test: Relative Potency %.
- Advanced Report: Resolved an issue, that no EC50 has been reported sometimes.
- Resolved a problem, that outlier detection has been deactivated for control lines with dose value ‘0’.
- Resolved a problem, that the range optimizer did not ensure the minimal number of steps, if whole steps has been removed by being marked as technical outliers.

10.5.2 Dichotomous Assay

- Report: The report generation problem for standard samples without data has been corrected.

10.5.3 Control Chart

- Fixed a problem that resources for the control chart could not be resolved.
- A problem with the aggregation of the C parameter (restricted regression) has been corrected.
- Resolved an issue, that control charts are missing information.

11 Biological assay Package 23 Release Notes

11.1 Document Package: Biological Assays

Version: 23 (Build 875) (Previous Version: 22).

11.2 New

11.2.1 Combination of Assay Results

- All non-integer valued assay and sample suitability tests support now the optional element rounding with possible values 'No Rounding', '0 decimal places', '1 decimal places', ..., '10 decimal places'. If this is defined the value(s) compared to margins or critical values are rounded to the specified number of decimal places.
- 'Test on Mean of CV (%)' is supported now.

11.2.2 Control Charts

- Revision of the Graphics
  - Separated axis
  - Optional horizontal lines with additional small lines in 10%-steps of the interval
  - Optional vertical lines
  - Optional legend (the amount of assay elements determines the size of the legend and the scale on the y-axis (simply speaking: range + 5%-steps of the range up to 2*range). Furthermore, it determines the number of columns (either one or two)).
  - Label of the x-axis (default: Index)
  - Label of the y-axis
  - Label of the response unit
  - Choice of data point plotting as circles or lines (In case of n>500: lines)

11.2.3 Dichotomous Assays

- Revision of the Graphics
  - Separated axis
  - Optional horizontal lines
  - Optional vertical lines
  - Optional legend (the amount of assay elements determines the size of the legend and the scale on the y-axis. Furthermore, it determines the number of columns (either one or two)).
  - Small tick marks if Display Lines is TRUE
  - Choice for names of the tick marks on the x-axis: absolute dose, transformed relative dose, untransformed relative dose
  - Label of the x-axis (default: Dose)
  - Label of the y-axis
  - Label of the response unit
- All non-integer valued assay and sample suitability tests support now the optional element rounding with possible values 'No Rounding', '0 decimal places', '1 decimal places', ..., '10 decimal places'. If this is defined the value(s) compared to margins or critical values are rounded to the specified number of decimal places.
- It is now possible to choose between 'Confidence Level (%)' and 'p'. If 'p' is selected, the test evaluation is based on the comparison of the p value to the specified margin. Otherwise the test evaluation is based on the comparison of the critical value of the considered distribution.

11.2.4 Quantitative Response Assays

- Revision of the Graphics
  - Optional display part for Control Line
  - Separated axis

  - Optional horizontal lines
  - Optional vertical lines
  - Optional legend (the amount of assay elements determines the size of the legend and the scale on the y-axis (simply speaking: range + 5%-steps of the range up to 2*range). Furthermore, it determines the amount of columns (either one or two)).
  - Small tick marks if Display Lines is TRUE
  - Choice for names of the tick marks on the x-axis: absolute dose, transformed relative dose, untransformed relative dose
  - Choice for names of the tick marks on the y-axis: transformed relative dose, untransformed relative dose
  - Dotted lines between data points which are not in range
  - Label of the x-axis (default: Dose)
  - Label of the y-axis (default: Response)
  - Label of the response unit
- The optional element 'Test Name' is now available for all assay and sample suitability tests. Test names have to be unique and are used for defining conditional tests.
- The optional element 'Conditional Evaluation' is supported for all assay and sample suitability tests. It has the sub elements 'Test Reference' and 'Evaluation Condition'. The 'Test Reference' contains the test name of the test, which is used as condition for the evaluation (test condition) of the actually considered test (the conditional test). If the evaluation condition is set to 'Referenced Test Passes', the conditional test is only evaluated, if the test condition is passed. If the evaluation condition is set to 'Referenced Test Failed', the conditional test is only evaluated, if the test condition is failed. Conditional testing is only possible if there is a unique mapping of test conditions to conditional tests. Otherwise the calculation is aborted with an error.
- All non-integer valued assay and sample suitability tests now support the optional element rounding with possible values 'No Rounding', '0 decimal places', '1 decimal places', ..., '10 decimal places'. If this is defined the value(s) compared to margins or critical values are rounded to the specified number of decimal places.
- It is now possible to choose between 'Confidence Level (%)' and 'p'. If 'p' is selected, the test evaluation is based on the comparison of the p value to the specified margin. Otherwise the test evaluation is based on the comparison of the F ratio to the critical value of the Fisher F-distribution.
- 'Additional Test: Sum of Squares Non-Parallelism' is supported now.
- The 'Additional Test: Value of Parameter Estimates' now supports 'Difference of Lower Asymptotes', 'Ratio of Slopes', 'Ratio of Upper Asymptotes', 'Ratio of Lower Asymptotes', 'Dynamic Range / Asymptote Range' and 'Signal to Noise / Asymptote Ratio' as parameters.
- The 'Additional Test: Maximal Sequence Step CV (%)' supports now an optional lower margin.
- The EC 50 is now reported in the advanced detailed report.

11.2.5 Equivalence Margin Development

- Margins for 'Equivalence Test (Difference of Parameter Estimates)' and 'Equivalence Test (Ratio of Parameter Estimates)' for parameter 'Dynamic Range' are now supported now.
- Upper margin for 'Additional Test: Sum of Squares Non-Parallelism' is supported now.

11.3 Changed

11.3.1 Combination of Assay Results

- The comparison for deriving the passed/failed status of a suitability test now always includes 'equal' in the 'is passed' case.

11.3.2 Dichotomous Assays

- The comparison for deriving the passed/failed status of a suitability test now always includes 'equal' in the 'is passed' case.

11.3.3 Equivalence Margin Development

- Samples with status 'Failed' or 'Rejected' are not anymore included in the margin estimation for the 'Additional Test: Sum of Squared Non-Linearity'.
- Report and dashboard has been revised.

11.3.4 Quantitative Response Assays

- The comparison for deriving the passed/failed status of a suitability test now always includes 'equal' in the 'is passed' case.
- The confidence level used for the evaluation of equivalence test is now reported in the result section of the test.
- The dashboard now shows the assay results in the order of the assay element definition.

11.4 Fixed

11.4.1 Dichotomous Assays

- The use of '<' and '&' are used in assay element names does no longer lead to an abort of the calculation routine.

11.4.2 Quantitative Response Assays

- The use of '<' and '&' are used in assay element names does no longer lead to an abort of the calculation routine.
- Infinite confidence limits are now reported in the results of equivalence tests.
- Midpoint of range calculation has been corrected. (Note: So far no report exists, that contains this value.)
- The calculation of the EC 50 in case of the 5-parameter logistic model has been corrected. (Note: So far no reports of the standard packages reported this value.)
- The calculation of the standard error for the asymptote difference has been corrected. The affected suitability tests are 'Equivalence Test (Difference of Parameter Estimates) - Parameter: Dynamic Range', 'Equivalence Test (Ratio of Parameter Estimates) - Parameter: Dynamic Range', 'Equivalence Test: Difference of Asymptotes' and 'Equivalence Test: Scaled Range of Asymptotes'.

12 Biological assay Package 22 Release Notes

12.1 Document Package: Biological Assays

Version: 22 (Build 843) (Previous Version: 21).

12.2 New

12.2.1 Quantitative Response Assays

- The assay element specific lines for 'Non-Linearity (Lack of Fit)' are printed in the ANOVA table of the detailed report and the advanced report. The corresponding rows are labeled by the assay element name.
- The default value for 'ANOVA with consideration of additional factors' is now 'false'.

12.3 Changed

12.3.1 Quantitative Response Assays

- 'Additional Test: Sum of Squares Non-Linearity (Assay Element)' has been added to the test system.
- 'Additional Test: Minimal R^2 (Assay Element)" has been added to the test system
- 'Equivalence Test (Difference of Parameter Estimates)' for the 'Dynamic Range' has been added to the test system,
- 'Equivalence Test (Ratio of Parameter Estimates)' for the 'Dynamic Range' has been added to the test system.
- 'Data Selection Schemes' now has an optional child element 'Quality Weight' with possible choices 'Coefficient of Determination', 'F-Ratio Regression' and 'Slope'. The default value is 'Coefficient of Determination'. This controls the quality weight used for range optimization.
- 'Analyze as multiplex assay' has been renamed to 'Simultaneous Regression'.

12.4 Fixed

12.4.1 Quantitative Response Assays

- The assay suitability and sample suitability tests section of a new quantitative response assay document do not contain any test definitions.
- The R^2 value is now printed in the report for nonlinear models too.

13 Biological assay Package 21 Release Notes

13.1 Document Package: Biological Assays

Version: 21 (Build 829) (Previous Version: 20).

13.2 Changed

13.2.1 Combination of Assay Results

- Weights for data rows not entering the calculation of the combined potency are now calculated and displayed in the report.

13.2.2 Quantitative Response Assays

- The help texts for the test system have been revised.

13.3 Fixed

13.3.1 Combination of Assay Results

- The combination calculation for slope ratio assays now correctly uses the arithmetic mean instead of the geometric mean in data aggregation mode.
- Units for the absolute potency are now transferred correctly to the combination document for quantitative response assays.

13.3.2 Quantitative Response Assays

- The calculation no longer terminates with an unexpected error if some non-standard characters (like " or ') have been used in assay element names.
- In rare cases the non-linear fit method detected a solution with interchanged asymptotes and inverted sign of the hill-slope in case of the 4-parameter fit. It should be noted, that this is also a valid result of the fit and this does not affect the relative potency. However, this result has some side effects regarding suitability tests. The system now correctly detects this interchanged results and restarts optimization with an optimized set of start estimates.
- The calculation no longer terminates with an unexpected error, if 'Additional Test: Relative Potency Range (%)' is defined with scope 'Standard Only'.
- The 'Additional Test: Maximal Sequence Step CV (%)' now takes outliers into account.
- The calculation no longer terminates with an unexpected error, if a sample with only one treatment has to be handled by the range optimizer. If such a configuration is selected as final configuration appropriate warning and info messages occur.
- If ‘Dilution Factors’ are defined in combination with ‘Absolute Potency: Defined by Stock Solution’ / ‘Absolute Potency: Defined by Raw Material’, the system now uses the ‘Estimated Potency (Stock Solution)’ / ‘Estimated Potency Raw Material’ as absolute potency for data aggregation (formerly ‘Potency Ratio (incl. Dilution Factors)’ has been used here).
- Data Source of acquired raw data is now printed in all reports.
- The dashboard now shows the correct absolute potency unit.
- File import of ‘.psf’-files now choses the correct settings for PLA 2.0 assays, where ‘Separate ANOVAs for each hypothesis (PLA 1.2 compatible)’ is selected.

13.3.3 Reports

- Incorrect formatting in the reports of some numbers between 1E6 and 1E7 with a mantissa of exactly 8 decimal digits has been corrected.
- The template information in reports is now only printed once.

14 Biological assay Package 20 Release Notes

14.1 Document Package: Biological Assays

Version: 20 (Build 816) (Previous Version: 19).

14.2 New

14.2.1 Combination of Assay Results

- Combination Calculation now supports dichotomous assays.
- Combination Calculation now supports control samples.
- Additional output for custom reports has been provided in the calculation result.

14.2.2 Control Charts

- The performance of the control chart update for large datasets has been significantly improved.

14.2.3 Dichotomous Assays

- p-Values for significance tests are now part of the output.
- Test on the signature state of document parts is now added for dichotomous assays.
- The Additional Test on User Variables is now added for dichotomous assays.

14.2.4 Quantitative Response Assays

- R-Squared value is provided now for nonlinear regression models.
- 'Additional Test: Minimal R-Squared' is supported for nonlinear models.
- Inclusion of the transformed 50 percent response for range optimization is supported now.
- In case of 50 percent inclusion when using the range optimizer, it is now possible to select the estimation method of the 50 percent response. Available options are arithmetic mean or the mean of minimal and maximal treatment mean.
- F-Test Quadratics with scope 'Assay' supports now slope ratio assays.
- The coefficient of determination estimation method can now be selected. Possible methods are 'default method' (implementing the used method of previous versions of the bioassay package), 'mean adjusted model' and 'intercept free model'.
- Additional output for custom reports has been provided in the calculation result. This includes output for reporting the ANOVA tables for the tests of Slope and Test of Linearity of PLA 1.2 and the signal to noise ratio calculated based on the observation data.

14.3 Changed

14.3.1 Basic Bioassay Protocol

- 'Template Selection Strategy' now replaces the option 'Force Common Replicate Number' with the possible choices 'Existing Replicates' and 'Existing Elements'.

14.3.2 Dichotomous Assays

- Linear predictor graphic has been revised.

14.3.3 Quantitative Response Assays

- In case of the three parameter model, the value of the fixed asymptote is now printed in the report.
- Revision of number formatting in the reports.

14.4 Fixed

14.4.1 Basic Bioassay Protocol

- Removed the not needed elements 'Absolute Potency' and 'Dilution Factors' for control line elements.
- Resolved some minor user interface and reporting issues.

14.5 Fixed

14.5.1 Combination of Assay Results

- Resolved an Issue, that some info, warning and error messages are reported twice.
- Resolved some minor user interface and reporting issues.

14.5.2 Control Charts

- Resolved an Issue, that some info, warning and error messages are reported twice.
- Resolved some minor user interface and reporting issues.

14.5.3 Dichotomous Assays

- Resolved an Issue, that some info, warning and error messages are reported twice.
- Messages for invalid assay definitions have been improved.
- Resolved an issue that led to the output of '/' for the absolute potency unit, in case of undefined units.
- Resolved some minor user interface and reporting issues.

14.5.4 Quantitative Response Assays

- In case of performing a Dixon outlier detection with 8 or more replicates, the outlier detection terminated with a warning and the outlier test result was ignored. This has been corrected.
- In case of 'optimization on' and 'identical range = false', the range optimizer did detect non-optimal solutions if there are more than on possible range selection candidates for a test sample.
- Resolved an issue, leading to a wrong severity level definition for the test on user variables.
- Resolved an issue, leading to a false degree of freedom in case of replaced outliers. This could only occur, if outlier replacement was activated.
- Resolved an issue, leading to a false degree of freedom for the denominator of F-Tests in case of confidence interval calculation method based on residual error of the restricted fit.
- Resolved an Issue, that some info, warning and error messages are reported twice.
- Resolved an issue that led to the output of '/' for the absolute potency unit, in case of undefined units.
- Messages for invalid assay definitions have been improved.
- Resolved some minor user interface and reporting issues.

15 Biological assay Package 19 Release Notes

15.1 Document Package: Biological Assays

Version: 19 (Previous Version 18). Note: Package Measurement Documentation Version 4 is a prerequisite for this package.

15.2 New

15.2.1 Quantitative Response Assays

- The 'Additional Test: Intermediate Dilution Potency' has been added to the test system.
- The 'Additional Test: Relative Potency Confidence Interval (%)' has been added to the test system.
- The 'Additional Test: Value of Parameter Estimate' has been added to the test system.
- The values 'Fold Difference' (upper minus lower asymptote) and 'Fold Ratio' for the restricted and the unrestricted regression model are provided for control charting.

15.3 Changed

15.3.1 Combination of Assay Results

- The combination calculation now ignores results with test status 'Excluded'. That means they do not appear in the report and (as in the previous versions) they will not enter the calculation.

15.4 Fixed

15.4.1 Basic Bioassay Protocol

- Resolved an issue that led in case of the assay element mode to generated quantitative response assay documents with test / control samples whose replicate number is not large enough to be included in the generated assay.

15.4.2 Control Charts

- Resolved an issue that prevented the generation of a control chart report.

15.4.3 Quantitative Response Assays

- The output of the F-Tests for the preparation term and the significance of slope contains the p-value.
- Resolved an issue that led to problems for generating the reports in case of multiplex assays.
- Resolved an issue that led to incorrect labels of the upper asymptote parameter for the unrestricted regression fit, when used in control charts.

16 Biological assay Package 18 Release Notes

16.1 Document Package: Biological Assays

Version: 18 (Previous Version: 17). Note: Package Measurement Documentation Version 4 is a prerequisite for this package.

16.2 New

16.2.1 Quantitative Response Assay

- A compact report is supported now.
- Potency Confidence Interval Calculation Method can be selected now. Possible choices are
  - Based on ANOVA Error: Calculates the potency confidence interval based on the selected ANOVA model. This is the method used in previous versions of the Biological Assay Package.
  - Based on Error of the Restricted Model: Calculates the potency confidence interval based on the residual error term of the restricted regression model.
- The tests on potency value and potency confidence interval can now also be calculated for the stock solution and raw material potency.
- A test for the maximal dose step coefficient of variation is supported now. An upper margin for the coefficients of variation can be defined.
- Tests for the potency result (e.g. test on the potency value) can now be performed for multiplex assays.
- Substance information of assay elements are now included in the report.
- Various new properties available for control charting and aggregation. Note: Existing assays need to be recalculated.

16.2.2 Combination of Assay Results

- A test for the percentual potency confidence interval is supported now.
- The χ^2-Homogeneity test can be defined and performed as suitability test.
- The definition of multiple section filters is now supported.
- It is possible to define substance informations for the combination groups. Therefore a group element has been introduced in the document content. When it references the group ID column of the dataset, substance informations defined for this combination group are printed out in the report part for this group.

16.2.3 Equivalence Margin Development

- The definition of multiple section filters is now supported.

16.2.4 Basic Bioassay Protocol

- The basic bioassay protocol has been completely revised. See manual.

16.2.5 Changed

16.2.6 Combination of Assay Results

- The fields 'Test Failed Message' and 'Tests Passed Message' have been removed.

16.3 Fixed

16.3.1 Quantitative Response Assay

- Resolved an error that led to printout of false p-values for the preparation term in a model row in the ANOVA table. Note: This error had no effect for the evaluation of suitability tests or potency.
- ANOVA model selection has been ignored for models with included control line. The pure error ANOVA has always been used.
- Several message errors fixed for incompletely specified assays.

16.3.2 Combination of Assay Results

- Several message errors fixed for incompletely specified assays.

17 Biological assay Package 17 Release Notes

17.1 Document Package: Biological Assays

Version: 17 (Previous Version: 14). Note: Package Measurement Documentation Version 4 is a prerequisite for this package.

17.2 Document Type: Combination of Assay Results

17.2.1 New

- All tests support a "scope". The scope field selects, whether the test is performed for the combination of relative or absolute potencies.
- The tests on potency value, potency confidence interval and potency range (%) are now available for absolute potencies.
- A Test on Sum of Weights has been added. A lower margin for the sum of weights (usually calculated for the homogeneity test) can be defined.
- The Test on Coefficient of Variation (%) has been added to the test section. An upper margin for the empirical coefficient of variation of the potency values can be specified.
- The Test on Number of Valid Assays has been added to the test section. Upper and/or lower margins can be specified. This test is especially useful if used in combination with the basic bioassay protocol for routine assays.
- The Test on (Log) Potency Range has been added to the test section. An upper margin can be specified for the range of the log potency values entering the combination calculation.
- The Test on (Log) Potency Confidence Interval Range has been added to the test section. An upper margin can be specified for the log potency confidence interval length of the combined potency.
- The logarithm base can now be specified in the analysis section. The selected logarithm base does only influence the results of the Tests on (Log) Potency Range and (Log) Potency Confidence Interval Range.
- A Test on Signature States has been added to the list of tests.

17.2.2 Fixed

- Resolved several errors, leading to non-comprehensible error messages in case of incomplete data/assay situations.
- Resolved several errors, where no report could be generated in case of incomplete data/assay situations.

17.3 Document Type: Quantitative Response Assay

17.3.1 New

- Dixon-, Grubbs- and Standard Deviation Outlier Test can now be used for control lines.
- The advanced settings now contain an optional field 'Replace Outliers'. If this is set to true, detected outliers are replaced by the mean of the remaining response values of the corresponding sequence step.
- The Additional Test: Maximal Number of Outliers now contains a field extent defining the evaluation range of the test. In case of 'Assay' all outliers of the assay are counted. In case of 'Assay Element' only the outliers of this assay element are counted. In case of 'Sequence Step' the maximum number of outliers for the sequence steps of the considered assay element are counted.
- The F-Test on Preparation has been added to the test section. This test tests the significance of the preparation term in the ANOVA table. The test is only available for the Linear Parallel Line Model and the Nonlinear 4-Parameter Model.
- The F-Test Difference of Quadratics (Assay Scope) has been added to the test section. This is a difference of model test, where the sum of squares quadratics (assay scope) is compared to the usual

sum of squares quadratics (for assay elements). This is a test for the support of legacy analytical methods.
- The F-Test Quadratics (Assay Scope) has been added to the test section. To perform this test, a quadratic model is fitted to the data of the whole assay simultaneously (in contrast to the usual F-Test Quadratics, where only the data of one assay element is used). This is a test for the support of legacy analytical methods.
- The Test on User Variable has been added to the test section. This test allows to test for variables and their values. It is useful in complex workflow setups.

17.3.2 Changed

- The additional fit of the 4-parameter-model with included control line is now performed including the control line values. The procedure used in previous versions ignored these values as in the Slope Ratio model. The new approach is more comprehensible. The result of this fit us used to perform the Non-Parallelism row of the ANOVA table (which directly influences the F-Test Non-Parallelism).

17.3.3 Fixed

- Resolved an error causing the range optimizer to select non-optimal configurations in some complex situations.
- Resolved several errors leading to non-comprehensible error messages in case of incomplete data / assay situations.
- Resolved several errors, where no report could be generated in case of incomplete data / assay situations.

18 Dose Response Analysis Package 1 Release Notes

18.1 Document Package: Biological Assays

Version: 1 (Previous Version: -). Note: Package Measurement Documentation Version 4 is a prerequisite for this package.

The Dose Response Analysis Package is a new Biostatistical Package available for PLA 3.0.5 and above. It is included in the PLA License (no additional purchase is required).