Data Integrity Guide

Data Handling
SOP Guidance
Practical Examples

Secure Your Measuring Processes

With LabX Software

METTLER TOLEDO

Editorial

Dear Reader,

One of the primary motivations driving organizations to purchase a LIMS, ELN or LES (collectively, Laboratory Informatics Systems, LIS) is the appeal of connecting laboratory instruments to them for electronic data collection. When a laboratory instrument is directly connected for electronic data capture, the costs in time, labor and potential error associated with manual transfer of data are essentially eliminated. However, even with these compelling advantages, many instruments and systems still remain unconnected to a network and data entry and transfer are largely handled manually.

Manual data transcription and report creation keep the laboratory analyst from focusing on the science. Transcribed data is frequently missing important elements, as well as the traceability needed to satisfy internal quality management and regulatory mandates. The end result is that time and revenue are lost due to the time and effort it takes laboratory analysts to resolve the situation by gathering missing data, re-transcribing results, documenting missing controls, and preparing reports.

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Content

1. An Enhanced Strategy for Data Integrity

1.1. Data Governance: Keeping Track of Your Results

For laboratories that must comply with Good Laboratory Practice, Good Manufacturing Practice or Good Automated Manufacturing Practice regulations (GLP, GMP, GAMP, respectively), a complete data-governance strategy must typically be designed and implemented. Data governance includes four components—data integrity, data traceability, data security and data quality—as depicted below:

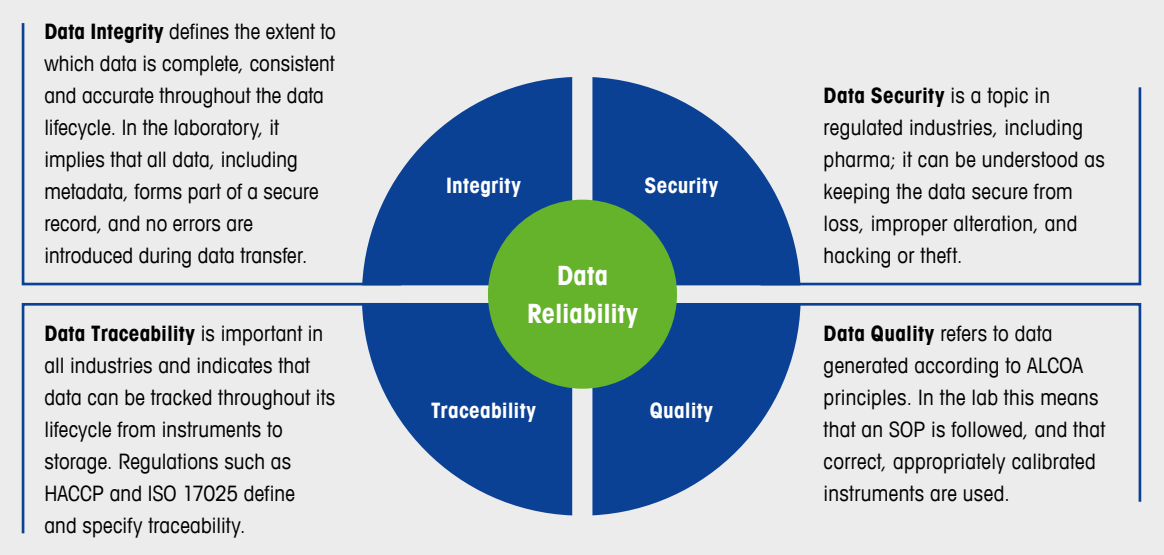


Figure 1: Data integrity is a component of a comprehensive data-management strategy.

1.2. Data Integrity

In 2017, 65% of warning letters issued by the US Food and Drug Administration (FDA) were due to lack of data integrity, most often data incompleteness; when not working compliantly, the consequences to an organization may rise to the level of import bans, product recalls, and even the closure of production facilities.

To ensure data integrity, organizations must maintain records or documented evidence of all relevant analyses. These should be available for checking by a second person, as well as for audits. Storing results is not enough; each result set must be complete and include all relevant metadata, as defined by the ALCOA+ framework:

ALCOA+	Meaning
1. **A**ttributable	• "Attributable" means information is captured in the record so that it is uniquely identified as executed by the originator of the data (e.g. a person or a computer system).
2. **L**egible	• The term "legible" refers to the requirement that data is readable and understandable, and allows a clear picture of the sequencing of steps or events in the record so that all GxP activities conducted can be fully reconstructed by the people reviewing these records at any point during the records retention period set by the applicable GxP.
3. **C**ontemporaneous	• "Contemporaneous data" means data recorded at the time it is generated or observed.
4. **O**riginal	• "Original" record: Data as the file or format in which it was originally generated, preserving the integrity (accuracy, completeness, content and meaning) of the record, e.g. original paper record of manual observation, or electronic raw data file from a computerized system. • Written observation or printout or a certified copy thereof. • Electronic record including metadata of an activity.
5. **A**ccurate	• Data is correct, truthful, complete, valid and reliable.
6. Complete	• All data from an analysis including any data generated when a problem is observed and resolved. For hybrid systems, the signed paper output must be linked to the underlying electronic records used to produce it.
7. Consistent	• All elements of the analysis such as the sequence of events follow on, and data files are date and time stamped in the expected order.
8. Enduring	• Recorded on authorized media, e.g. laboratory notebooks, numbered worksheets for which there is accountability or electronic media.
9. Available	• The complete collection of records can be accessed or retrieved for review and audit or inspection over the lifetime of the record.

Table 1: The ALCOA+ framework outlines criteria for data integrity.

Implementing measures that support data integrity in the laboratory is a crucial component of adherence to GMP/GAMP/GLP; following the ALCOA+ framework maximizes an organization's readiness for audits.

1.3. Daily Challenges in the Laboratory

The laboratory analyst typically follows standard operating procedures (SOPs) for each analysis, documenting the complete process and recording the results. While many labs have turned toward Laboratory Information Management Systems or Electronic Laboratory Notebooks (LIMS or ELNs, respectively) with the idea of replacing manual workflows, these systems are designed primarily to aggregate results from an array of analytical tests rather than to automate or document benchtop workflows, or to bind instrument metadata to a measurement.

As many organizations have discovered, the workflows behind benchtop analytical instruments (e.g. balances, titrators, pH meters), and the associated results, instrument information, user information and method applied, as well as other metadata, are much more complex than just the transfer of a few parameters. Complicating matters further, GLP/GMP and regulations and standards from the FDA (21 CFR Part 11), EU (Annex 11) and Internal Organization for Standardization (ISO; e.g. ISO 17025) have recognized both the advantages and the limitations of electronic data systems, and have increasingly established further controls for the use of such systems all the way down to benchtop instruments. Comprehensive consideration of analytical needs and compliance requirements should therefore be undertaken when selecting solutions to integrate and automate the laboratory bench.

Taking the example of a weighing "loss on drying" application where multiple, sequenced, weighing steps, as well as calculations and sample tracking, must be accomplished, capturing only limited measurement data electronically without metadata (e.g. the instrument, user, tare vessels, sample qualitative data, calibration history, SOP, method version, etc.) leaves the measurement without context and misses the objective. It is soon discovered that the process cannot be effectively managed without some degree of workflow interaction with the balance itself.

1.4. Finding the Best Approach

To ensure careful, accurate and complete data records that are archived and managed compliantly, the most effective solution is a ready-made, configurable software package that drives workflow SOPs directly through the instruments implicated. Ideally, such software should offer automatic, integrated instrument management and data capture functionalities that improve productivity and efficiency by centering the work on the instrument. With the expertise gained as a single-brand provider of the most frequently used laboratory benchtop instruments, METTLER TOLEDO offers two such software platforms for balances and analytical instruments to deliver a single-vendor solution to the benchtop integration challenge.

These software packages, LabX® and STAR^{e}, and how they can support GLP/GMP and compliance with data-integrity regulations, are outlined in the following sections.

1.5. LabX—A Software Platform to Increase Productivity, Support Compliance and Reduce Complexity

LabX is a unified software platform designed to manage your METTLER TOLEDO instruments, together with the data they produce. With full on-screen user guidance, this easy-to-use software package increases productivity in the laboratory while facilitating regulatory compliance. Designed to meet the needs of any company, up to the largest global enterprise, LabX incorporates a broad range of features that cover your most advanced applications, as well as enabling automatic data export to your LIMS.

1.5.1. How LabX Supports Laboratory Productivity

Multiparameter Measurements—Workflow Support across Instruments
Many quality control applications require the simultaneous determination of multiple analytical parameters. To smooth users' operations, METTLER TOLEDO lab instruments such as titrators, density meters and pH meters can be linked together to create a multiparameter measurement system that provides a fully documented, secure workflow across all instruments required.

The workflow is orchestrated by the LabX laboratory software, which permits users simply to follow instructions directly on the screen of the relevant instrument. Data derived from each individual analysis is stored centrally in LabX's database and assigned to the correct sample. Thus, storage, review and reporting of the complete dataset associated with a specific sample are easy and secure.

Asset Management—Keep Control over Instrument Status
Instruments that are ready to measure form the basis for high-quality results. What this entails can vary depending on instrument type and the requirements for accuracy. Balances, as an example, must be leveled prior to measurement, while pH sensors require regular calibration with correct buffer solutions. LabX keeps track of networked instruments and informs users if any actions, including service, are required. Status information is displayed directly on each instrument's screen, and an overview of the status of all connected instruments is also accessible from the PC. This allows the user to see instrument uptime, and scheduled or unanticipated downtime, at a glance.

1.5.2. How LabX Supports Fulfillment of Relevant Standards

Secure Processes—Make Sure Your SOPs Are Followed
Depending on the quality standards relevant to tested products, companies develop measurement workflows to match requirements and define these workflows in SOPs. SOPs are often available to users as printouts—which may give rise to mistakes, e.g. in the event that important steps are missed or data records incomplete or wrong.

LabX, in contrast, guides users step by step at the instrument, ensuring SOPs are followed to the letter. In addition, it ensures the automatic collection of complete data, including metadata. And once an SOP is defined in LabX, it can easily be transferred to any connected instrument or LabX installation.

Electronic Record-Keeping—Ensure Data Integrity
Measurement data, as the basis for important decisions, must not only be accurate and repeatable, but traceable and easily accessible by stakeholders so that results can be reproduced in case of any issues. Collecting measurement data electronically eliminates the risk of transcription mistakes and likewise ensures data is gathered in a consistent and complete way. LabX collects data from connected instruments following the requirements for data integrity outlined in the ALCOA+ framework, and permits the simple retrieval of any dataset via various filter functionalities.

Electronic Signatures and Audit Trail—Comply with Strict Regulations
The United States FDA and the European Commission have both defined standards for the conditions under which regulated companies can submit electronic records in lieu of paper documents. While these standards were initially developed for pharmaceutical manufacturers, they remain valid in other industries where an audit trail is essential.

Electronic records compliant with the FDA and European standards can replace paper records for submission, inspection and archiving purposes. The regulations define the measures that must be in place to ensure the integrity, trustworthiness and reliability of such electronic records.

The regulations define and require three types of controls:

1. **Administrative controls**, e.g. the definition of policies such as the identification of individuals and nonrepudiation of electronic records.
2. **Procedural controls**, e.g. SOPs for using and maintaining a system.
3. **Technical controls**, e.g. functions built into the software such as security and access to the system, as well as the audit trail. No instrument or software-based system alone can be compliant.

For compliance with regulations, all three of the above controls must be implemented.

21 CFR Part 11 ("Electronic Record; Electronic Signatures") defines criteria for acceptance by the FDA of electronic records and signatures on electronic records as equivalent to paper records and handwritten signatures. It defines the criteria by which electronic records and electronic signatures are considered trustworthy, reliable and equivalent to their paper analogs. It requires FDA-regulated industries to implement controls, audit trails, validations, electronic signatures and documentation of software systems involved in processing electronic data.

While 21 CFR Part 11 applies to companies doing business with the USA, the European Commission has created, for computerized systems, Annex 11 ("Computerised Systems") to Volume 4 of GMP for the European market.

Similar to the FDA regulations, Annex 11 applies to all forms of computerized systems used where GMP regulations apply. Annex 11 applies when computerized systems replace manual operations; there should be no resultant decrease in product quality, process control or quality assurance as well as no process-related risks.

21 CFR Part 11 and EU Annex 11 are complex regulations, requiring the implementation of technical, administrative and procedural controls to ensure compliance. LabX integrates all necessary technical controls, making it ready to support a lab in regulatory compliance. The LabX system, together with the validation products and services offered by METTLER TOLEDO, takes you most of the way. With only a few administrative and procedural controls, compliance is assured.

21 CFR Part 11	**LabX**
Controls for Closed Systems Persons who use closed systems to create, modify, maintain or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, integrity, and, when appropriate, the confidentiality of electronic records, and to ensure that the signer cannot readily repudiate the signed record as not genuine. Such procedures and controls shall include the following: 11.10 (a) Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.	✓
11.10 (b) The ability to generate accurate and complete copies of records in both human readable and electronic form suitable for inspection, review and copying by the agency. Persons should contact the agency if there are any questions regarding the ability of the agency to perform such review and copying of the electronic records.	✓
11.10 (c) Protection of records to enable their accurate and ready retrieval throughout the records retention period.	✓
11.10 (d) Limiting system access to authorized individuals.	✓
11.10 (e) Use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information. Such audit trail documentation shall be retained for a period at least as long as that required for the subject electronic records and shall be available for agency review and copying.	✓
11.10 (f) Use of operational checks to enforce permitted sequence of steps and events, as appropriate.	✓
11.10 (g) Use of authority checks to ensure that only authorized individuals can use the system, electronically sign a record, access the operation or computer system input or output device, alter a record, or perform the operation at hand.	✓
11.10 (h) Use of device (e.g. terminal) checks to determine, as appropriate, the validity of the source of data input or operational instruction.	✓
11.10 (i) Determination that persons who develop, maintain, or use electronic record/electronic signature systems have the education, training, and experience to perform their assigned tasks.	✓
Signature Manifestations 11.50 (a) Signed electronic records shall contain information associated with the signing that clearly indicates all of the following: (1) The printed name of the signer; (2) The date and time when the signature was executed; and (3) The meaning (such as review, approval, responsibility, or authorship) associated with the signature.	✓

11.50 (b) The items identified in paragraphs (a)(1), (a)(2), and (a)(3) of this section shall be subject to the same controls as for electronic records and shall be included in human readable form of the electronic record (such as electronic display or printout).	✓
Signature/Record Linking 11.70 Electronic records and handwritten signatures executed to electronic records shall be linked to their respective electronic records to ensure that the signatures cannot be excised, copied, or otherwise transferred to falsify an electronic record by ordinary means.	✓
General Requirements 11.100 (a) Each electronic signature shall be unique to one individual and shall not be reused by, or reassigned to, anyone else.	✓
Electronic Signature Components and Controls 11.200 (a) Electronic signatures that are not based on biometrics shall: (1) Employ at least two distinct components such as an identification code and a password. (i) When an individual executes a series of signings during a single, continuous period of controlled access, the first signing shall be executed using all electronic signature components; subsequent signings shall be executed using at least one electronic signature component that is only executable by, and designed to be used only by, the individual. (ii) When an individual executes one or more signings not performed during a single, continuous period of controlled system access, each signing shall be executed using all of the electronic signature components.	✓
11.200 (b) Electronic signatures that are not based on biometrics shall: (2) Be used only by their genuine owners; and (3) Be administered and executed to ensure that attempted use of an individual's electronic signature by anyone other than its genuine owner requires collaboration of two or more individuals.	✓
Controls for Identification Codes/Passwords 11.300 Persons who use electronic signatures based upon use of identification codes in combination with passwords shall employ controls to ensure their security and integrity. Such controls shall include: 11.300 (a) Maintaining the uniqueness of each combined identification code and password, such that no two individuals have the same combination of identification code and password.	✓
11.300 (b) Ensuring that identification code and password issuances are periodically checked, recalled or revised (e.g. to cover such events as password aging).	✓
11.300 (c) Following loss management procedures to electronically de-authorize lost, stolen, missing, or otherwise potentially compromised tokens, cards, and other devices that bear or generate identification code or password information, and to issue temporary or permanent replacements using suitable, rigorous controls.	✓
11.300 (d) Use of transaction safeguards to prevent unauthorized use of passwords and/or identification codes, and to detect and report in an immediate and urgent manner any attempts at their unauthorized use to the system security unit, and, as appropriate, to organizational management.	✓

Table 2: 21 CFR Part 11.

EU GMP Annex 11	LabX
6. Accuracy Checks For critical data entered manually, there should be an additional check on the accuracy of the data. This check may be done by a second operator or by validated electronic means. The criticality and the potential consequences of erroneous or incorrectly entered data to a system should be covered by risk management.	✓
8. Printouts 8.1 It should be possible to obtain clear printed copies of electronically stored data.	✓
8.2 For records supporting batch release it should be possible to generate printouts indicating if any of the data has been changed since the original entry.	✓
9. Audit Trails Consideration should be given, based on a risk assessment, to building into the system the creation of a record of all GMP-relevant changes and deletions (a system generated "audit trail"). For change or deletion of GMP relevant data the reason should be documented. Audit trails need to be available and convertible to a generally intelligible form and regularly reviewed.	✓
12. Security Physical and/or logical controls should be in place to restrict access to computerized system to authorized persons. Suitable methods of preventing unauthorized entry to the system may include the use of keys, pass cards, personal codes with passwords, biometrics, restricted access to computer equipment and data storage areas.	✓
14. Electronic Signature Electronic records may be signed electronically. Electronic signatures are expected to: a. Have the same impact as hand-written signatures within the boundaries of the company, b. Be permanently linked to their respective record, c. Include the time and date that they were applied.	✓

Table 3: EU Annex 11.

1.5.3. How LabX Supports Reduction of System Complexity

Computer System Validation—Ensure Your Measurement System Is Fit for Purpose
The goal of computer system validation (CSV) is to provide documented evidence that the computerized measurement system is suitable for its intended use. CSV is required by various standards and typically represents a significant part of the overall budget for a digitalization project.

By connecting many instruments to the same software installation, validation efforts can be reduced significantly. With LabX, the CSV for up to 30 instruments takes no longer than a single CSV (approximately 3 to 6 months).

METTLER TOLEDO offers comprehensive support with:
- Project consulting and support (global team)
- User requirement sheet (URS) template
- Equipment qualification packages (EQPac)
- Local user training and application support
- Measurement uncertainty (MuPac) calculations (titration only) with comprehensive report
- Release notes to keep up-to-date

For detailed information on cost-effective computer validation for ensuring compliance of electronic records, please consult METTLER TOLEDO's series of webinars dedicated to this topic.

Simpler Integration and Maintenance—A Single Software for All Instruments
Connecting different instruments to a single software platform not only reduces effort toward system validation but affords many other benefits. Central management of all your measurement data, assets, users and methods makes completion of your daily tasks very efficient.

Computerized measurement systems often need to be integrated into overall software systems such as LIMS. Reducing the number of integration interfaces minimizes maintenance efforts; LabX provides all functionalities required for various methods of integration and supports compatibility of connected instruments with every software or firmware update, ensuring continuity of your specific system.

In a LabX system, no computer or tablet PC is needed on or near the bench. Driven from LabX, the balance or instrument touchscreen delivers real-time, step-by-step workflow guidance to the user according to the lab's own SOPs. SOPs are easily configured with the flexible workflow tool, which takes advantage of the balance and instrument-specific features uniquely present in each model's firmware.

When ready to begin work, the analyst simply touches a shortcut or selects a desired workflow from a selection on the balance or instrument. When complete, data can be analyzed in LabX on a networked PC in the lab or office, reports generated, and data sent to the LIMS as .csv, .xml or via a web services API.

		LabX				
	Lab information systems (LIS) direct to instrument	Drop transfer	.pdf transfer	Peripheral communication	Auto import/export	API web services
Full bi-directional data transfer	–	–	–	–	–	•
Control complete process from LIS or instrument	–	–	–	–	–	•
Connect LIS ID to sample data	–	–	–	–	•	•
Interface with data systems and inventory	–	–	–	•	•	•
Metadata (important sample and instrument data)	–	–	•	•	•	•
Integrate with any system	–	–	•	•	•	•
User management	–	•	•	•	•	•
Updated firmware and instruments supported	–	•	•	•	•	•
Traceability	–	•	•	•	•	•
SOP guidance	–	•	•	•	•	•
Instrument control	–	•	•	•	•	•
Support regulation compliance	•	•	•	•	•	•
Improve efficiency	•	•	•	•	•	•
Remove transaction errors	•	•	•	•	•	•

Table 4: Variety of integration possibilities.

	Manual data transfer	Work on the instrument according to a written SOP. Make calculations manually, write results in a lab notebook, and enter the values into the instrument manually. Write results in lab notebook. Manually enter the results and information into LIS. Store lab notebooks for future audits.
	Lab Information Systems (LIS) direct to instrument	LIS vendor or integration company programs custom code into each instrument. Result values available typically when pressing "Print" on instrument. Changes to instruments or updates to firmware or software often require reprogramming of custom code and revalidation efforts.
LabX	Drop transfer	Using the "Transfer Data" function within a method; during the workflow data is transferred into an open cursor position in Excel. Data can be sent to Excel; all metadata is available (e.g. instrument information, user information, results…).
LabX	.pdf transfer	As flexible and detailed as a report printed on a network printer, a .pdf report is created and stored in a folder on the network. Many LIS systems have the ability to read this .pdf data, import the files and input into their system.
LabX	Peripheral communication	Send and receive data from external systems during the workflow. Two-way communication between instruments.
LabX	Auto import/export	**Export:** Extensive metadata for results, products and sample series can be exported as a .csv or XML formatted file. The file can be configured in various ways (e.g. after electronic signature, only if results are with tolerance range, or simply automatically to any folder from which any other information system can import the file). **Import:** Files in .csv or XML format can be sent from most information systems for tasks, products, and sample series. LabX either manually or automatically runs or imports files as defined and required.
LabX	API webservices integration	Using common web service techniques, extensive data can be exchanged between LabX and other software systems, instruments and even mobile devices. Information, running methods and tasks, and collecting reports and complete data can be triggered by various external software systems or instruments at various points within a workflow. This is true bi-directional communication and connects the systems together as one. In practice users can create and start tasks from either the LIS or directly on the instrument touchscreen. All data flows back and forth through this expanded system network at multiple points, as required by the lab's working style.

Table 5: Definitions of the typical ways of transferring data to/from integrated systems.

1.6. STAR^{e}: A Modular Software Platform for Thermal Analysis Measurements and Their Evaluation

METTLER TOLEDO's STAR^{e} software enables the capture of comprehensive, high-quality data from thermal analysis techniques such as differential scanning calorimetry, thermogravimetric analysis, thermomechanical analysis and dynamic mechanical analysis, providing powerful tools to evaluate the resulting measurements. The software was developed following ISO 9001 guidelines and is modular, permitting the user to add to the functionalities present depending on the types of experiments and analyses to be performed, as well as the level of compliance required.

STAR^{e} includes the features necessary for a complete data integrity solution. Stored in a secure, relational database, electronic records are fully protected against modification, whether intentional or not. In addition, all evaluations performed on curves are automatically saved as copies with updated timestamps so as to preserve the original records.

The STAR^{e} software offers two options for data integrity (see also Table 6):

1. **Data Integrity Option**
   Relevant in any industry where quality is an important factor, as well as in academic research.
2. **21 CFR Part 11 Option**
   For pharmaceutical and food customers who must be compliant with given regulations, such as 21 CFR Part 11. This option includes the data integrity option.

The two STAR^{e} options are described below in more detail; consult our Thermal Analysis YouTube channel for videos highlighting various STAR^{e} modules, practical workflows for thermal analysis of various sample types, and additional information on methods for evaluation and interpretation of curves.

1.6.1. Data Integrity

With STAR^{e} SW v16.20, two new, important, functionalities have been added to the Data Integrity option:

- User groups
- Data classification

User Groups

The expanded Data Integrity software option, previously known as "User Rights", allows you to assign users to groups or projects. This enables configuration of the software for each specific user so that it matches the functional company organization as well as the (more dynamic) project organization.

If a user is correctly assigned to groups and projects, unauthorized viewing, access or modification of data is restricted.

This can be very important not only in companies but also in research environments where the newest data, for example prior to a publication, should only be accessible to a limited group of users.

Data Classification

Another new aspect of the Data Integrity option is the classification of data, which enables you to restrict data access still further.

This new possibility has been implemented so that almost everything proceeds automatically after configuration. In exceptional cases, you can manually change the default classification.

The new STARe Data Integrity software option therefore provides the following functions:
- User accounts for access control
- User roles to determine functionalities available to each user (= user profiles)
- User-group–specific data access
- Data classification to protect confidential data

1.6.2. 21 CFR Part 11

To meet more stringent compliance requirements, we offer the 21 CFR Part 11 option. This option provides the technical controls necessary to support compliance with 21 CFR Part 11 regulations governing electronic records and electronic signatures.

STARe has been designed to work as a closed system, such that system access is controlled by individuals who are responsible for the electronic records generated and archived within the system. Its key features are:
- User accounts for access control
- User roles to determine the functionalities available to each user (= user profiles)
- Electronic signatures that indicate the status of electronic records
- Audit trail that logs both change and system histories

1.6.3. Audit Trail

STARe includes both analysis and system audit trails for compliance and security. The analysis audit trail keeps detailed records of all significant changes of electronic data objects, documenting the creation, modification and deletion of any electronic record and tracking what, how, who, when, where and why:
- What was changed (indicates the record type)
- How it was changed (previous versus new values = record difference)
- Who made the changes (user and user name)
- When the change occurred (date and time of the change via computer-generated timestamp)
- Where the change was made (electronic record identification)
- Why the change was made (the reason, if given)

The system audit trail logs all system changes (login attempts, software updates, backup and restore, user account creation,…), enabling detailed oversight of any STARe system.

Further adding to STARe's ease of use and security is a series of filters that allow users to identify specific parts of the audit trail to facilitate review or inspection. Action, user, date and item (record type) filters can all be applied, for easy retrieval of a specific record or records.

	Data Integrity Option	**21 CFR Part 11 Option**	
Regulations	–	USA 21 CFR Part 11	Europe EU GMP Annex 11
More information can be found at:	▶ **www.mt.com/ta-dataintegrity**	▶ **www.mt.com/ta-cfr**	
Access control	•	•	
User rights	•	•	
Electronic signature	–	•	
Audit trail	–	•	

Table 6: The two STARe options at a glance.

1.7. STAReX: Added Security with a Link from LabX to STARe

In the LabX Server edition and v16.10 of STARe, the STAReX™ link between the software packages was introduced, enabling the transfer of weighing data directly to a thermal analysis instrument and further reinforcing data integrity for integrated workflows.

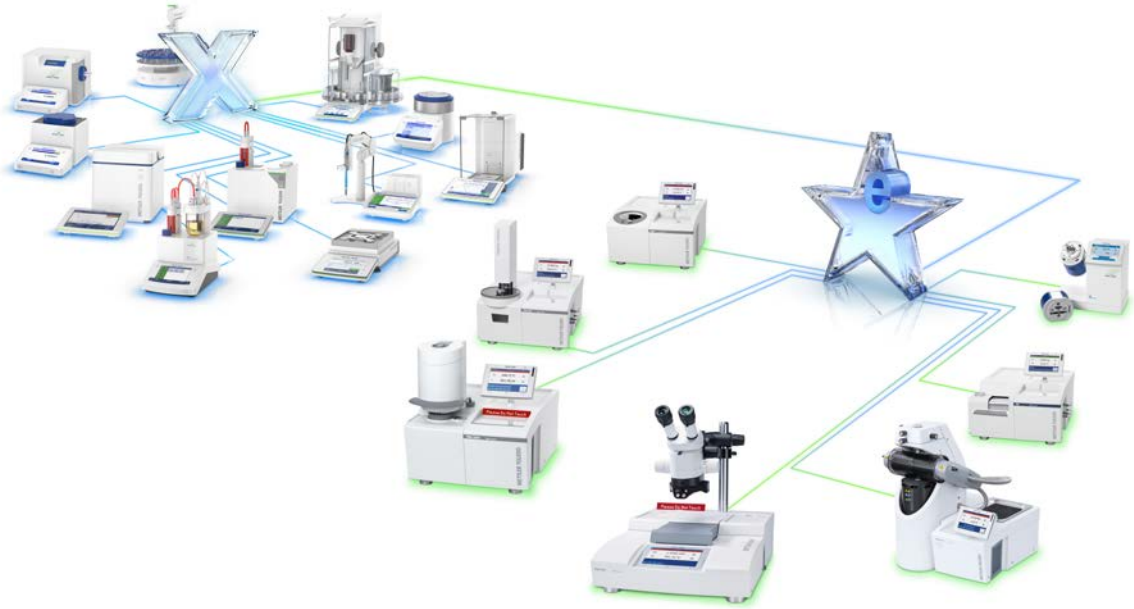


Figure 2: LabX and STARe networks linked together by STAReX.

Please see our videos on installing and using STAReX for more information.

1.8. System Validation

METTLER TOLEDO can assist with the installation and validation of LabX or STARe systems. Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ) are all available; service professionals can provide assistance with developing plans suited to your needs.

Please consult our website for LabX and STARe installation and validation options.

2. An Example for Weighing

2.1. The Way Many Labs Work Today

In this section we will look at how an analytical balance is used during a common laboratory procedure—the preparation of an analytical reference standard solution—and highlight where errors and problems might occur.

During this process, a reference standard is weighed out, transferred to a volumetric flask and dissolved, and the resulting solution brought to the appropriate volume. This is a typical use of an analytical balance in laboratories involved in quantitative analysis.

Preparation will be achieved, depending on the way the process is performed, using some of the following items:

- Analytical balance with or without thermal printer
- Laboratory notebook to record the work and summarize the results
- Calculator or spreadsheet software to calculate the concentration of reference standard (after adjustment for factors such as purity or conversion from salt form to base)
- LabX laboratory software to automate the process and record the results directly in the application's database. The software is operated using the balance touchscreen; an audit trail is maintained in the software, and reports will be signed electronically, with an option to print, if required.

2.1.1. Process Flow Figures Explained

Figures 3 to 5 in this guide are cross-functional process maps or "swimming lanes." Each of the lanes represents the work carried out by an item detailed above (the analytical balance, spreadsheet software, LabX, laboratory notebook, etc.). Activities are noted in the lane for the item in question: e.g., "weigh an external mass" or "tare the weighing vessel for the balance". Where the process crosses from one lane to another it represents an interaction between two lanes: e.g., "weigh a sample on the balance and record the observed balance weight in a laboratory notebook". The overall time for the process starts at the top of the figure and ends at the bottom.

2.1.2. Overview of Selected Weighing Processes

The three processes described in this chapter assume that there is an SOP or working instruction for the preparation of a nominal concentration of reference standard, and therefore the amount of reference material to be weighed is known. The instructions will typically indicate that an amount to be weighed must be within a range of acceptable values. Once the weight of the standard is known, an analyst will calculate the actual concentration, as opposed to the nominal concentration, of the solution.

If no instructions are available, the analytical scientist must prepare a reference solution from first principles. In this case an additional calculation step is required to determine the amount of standard to be weighed, as well as the volume that the substance must be dissolved in.

The processes also describe the vessel into which the reference standard is weighed. This can be a weighing boat or volumetric flask depending on the working practices of an individual laboratory. However, modern analytical balances allow the safe and ergonomic positioning of tare containers so as to avoid any intermediate containers that might introduce weighing errors. METTLER TOLEDO recommends the SmartGrid™ weighing pan and ErgoClips vessel holders.

2.2. Process 1: Weighing and Recording by Observation

Shown in Figure 3, below, is the weighing process flow for the reference standard in which values are recorded, by observation from the balance screen, in an analyst's laboratory notebook.

Subsequent calculations are performed using a handheld calculator, and also recorded in the analyst's lab notebook. The volumetric flask is labeled by hand to identify the solution, details of its preparation, and its expiry date.

- The process begins by outlining the procedure to be undertaken in the lab notebook and checking that the reference standard selected for preparation is correct.
- Next, the balance is checked with an external calibration mass. The balance and calibration standards used are recorded in the lab notebook by the analyst, then the weighing vessel is weighed and the balance tared.
- The reference material is weighed on the analytical balance and the reading on the screen observed and recorded by the analyst in the lab notebook.
- The vessel is then removed, and the balance cleaned for the next user. The reference material is transferred to an appropriately sized volumetric flask and liquid added to prepare the reference solution. The analyte is dissolved, and the solution then made up to volume.
- The flask is labeled by hand with the standard identification number, substance information, calculated concentration, name of the analyst who prepared the solution, storage conditions, and the dates of preparation and expiry.
- The analyst determines the actual concentration of the reference standard solution with a handheld calculator, taking into account relevant factors such as purity or water content. He or she reads the final value from the calculator display and transcribes it into the lab notebook, recording calculations and conversion factors used.
- The analyst checks the data and results, including repeating the manual calculations, and if correct signs the relevant pages of the lab notebook. If deviations from the procedure or instructions have occurred, the analyst must record them as well.
- A second person reviews the data and procedure to confirm their correctness, and then signs to approve the work. Should corrections be necessary, the first analyst undertakes them and returns for approval.

Manual Process without a Printer

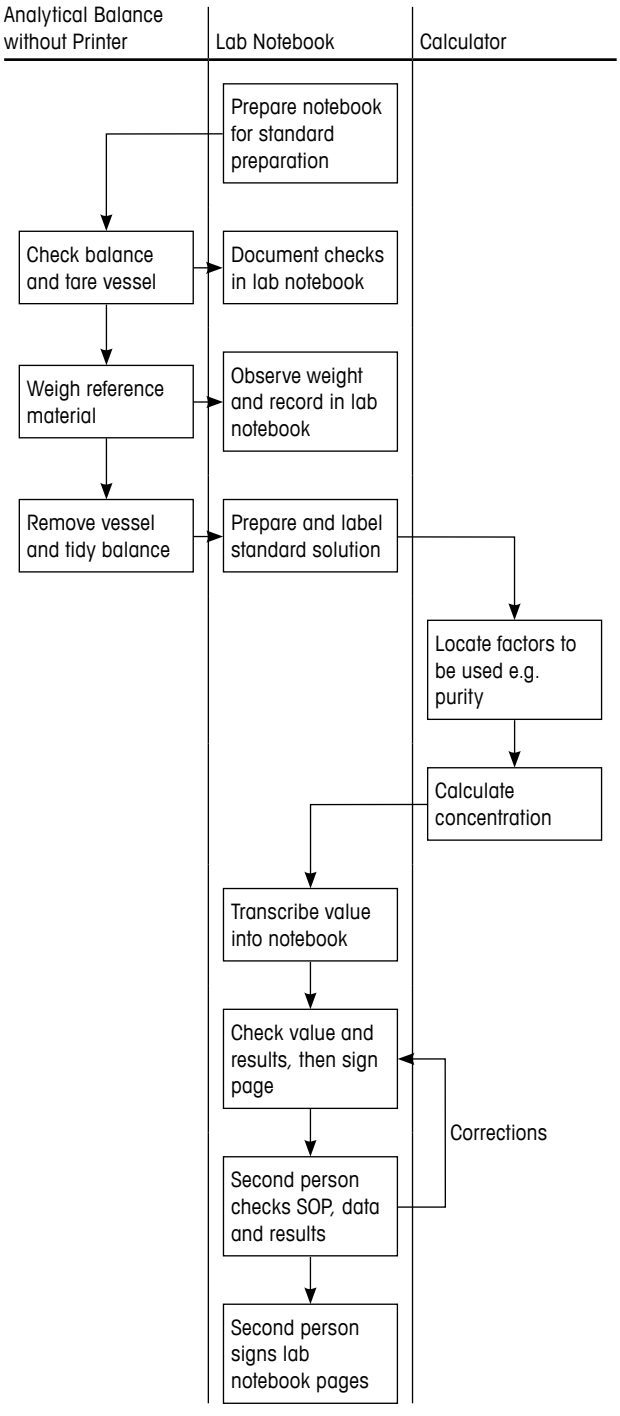


Figure 3: Cross-functional process workflow for manual observations from an analytical balance.

2.3. Possible Pitfalls of the Manual Workflow

Owing to the manual nature of the weighing process detailed above, error-prevention is critical. In the sections below, we outline operations particularly susceptible to error.

2.3.1. Transcription of Data and Error Checking Are Error-Prone

Quality standards (e.g. ISO 17025) and pharmaceutical industry regulations stipulate the "four eyes" principle: one person performs the work and a second, independent, person reviews it. This principle is based on the idea that four eyes are better than two. However, both the operation and the check are error-prone in their own right; typographical errors may be missed in the second person review, especially if the individual is under pressure with other tasks to perform.

2.3.2. Lack of a Data Audit Trail

No independent paper audit trail is generated during manual weighing and dilution operations; instead, the accuracy of the process depends on the ability of the analyst performing the work to correctly record the values displayed on the balance and calculator, and transcribe them into the laboratory notebook without error. While the calculator result can be replicated by keying in the data and performing calculations again, even when undertaken by highly trained humans it may be subject to error. What the brain thinks it has seen and recorded may not be the actual value on the balance or calculator; moreover, the second person cannot check the actual balance reading, which is the major failure point of this process.

2.3.3. Failure to Meet GLP, GMP and GAMP Regulatory Requirements

For laboratories that must comply with GLP, GMP and GAMP regulations, it is important to have records or documented evidence that can be checked by a second person and are also available for inspection. The method of working described in Figure 3 is unacceptable to FDA inspectors, as noted by this warning letter citation:

> Your firm **failed to ensure that laboratory records included complete data** derived from all tests necessary to assure compliance with established specifications and standards (21 CFR 211.194(a)). For example, **your firm did not retain any raw data related to sample weights and sample solution preparations for the HPLC assays** of <redacted> tablet batches <redacted> and <redacted> that you conducted on July 18, 2012. FDA Warning Letter, May 2013.

The major issue is that the balance result cannot be verified—in fact the analyst could just write down anything and say the work had been performed. Over 20 years ago the FDA advised their inspectors, when looking at weighing results from analytical balances and preparation of standard solutions, to:

> **Carefully examine and evaluate laboratory logs, worksheets and other records containing raw data such as weighings**, dilutions, the condition of instruments **and calculations**. **Note whether raw data is missing**, if records have been rewritten, or if correction fluid has been used to conceal errors. Results should not be changed without explanation. Cross-reference the data that has been corrected to authenticate it. [Ref 1]
>
> Review records of standard solution preparation to assure complete and accurate documentation. **It is highly unlikely that a firm can "accurately and consistently weigh" to the same microgram**. Therefore, data showing this level of standardization or pattern is suspect, and should be carefully investigated. [Ref 2]

To comply with GxP regulations and avoid intimidating questions from an inspector, a regulated laboratory should at minimum employ a printer attached to the balance to record the weights of reference standards and samples during the course of an analysis. The advantages of this approach from the perspective of regulatory compliance and laboratory efficiency will be reviewed in the next section.

2.4. The Way Labs Could Be Processing Data

To help eliminate sources of error, laboratory workflows should be automated. There are various possibilities, including:

1. Attaching a thermal printer to the analytical balance, while maintaining the rest of the items described in the previous section. Although the process is still manual, records that can be independently checked by a second person are generated. Thermal technology can print on both normal and thermal paper; the latter is very stable and has high resistance to plasticizers, oil, fat and water, generating a more robust paper trail that may be archived for up to 25 years. In addition, such printers are fast and quiet and, if required, can be used in a clean environment, as unlike paper printers they do not produce airborne dust.

2. Using LabX to convert a manual process to an electronic one. The application is configured once to prepare reference standards and perform the requisite calculations. To aid compliance, all user actions are recorded in the audit trail and electronic signatures are used by the analyst and a second individual to review and approve the results. This makes the process fully electronic and collects complete data in a single location.

2.4.1. Process 2: Weighing with a Printer Attached to the Balance

As shown in Figure 4, weighing workflows can be adapted to include a thermal printer attached to the balance to record results contemporaneously; a validated spreadsheet can likewise replace the handheld calculator. This improves efficiency while concomitantly reducing the error risk of the manual process, with the added bonus of a regulatory or quality paper trail.

- As was the case for the manual weighing workflow, the procedure is recorded in the analyst's laboratory notebook, and the correct reference standard selected.
- Next, the balance is checked and the weighing vessel is weighed and tared. The results are printed out, together with the date and time of the activity.
- The reference standard is weighed on the analytical balance and the reading printed, avoiding a manual transcription step. The vessel is removed and the balance cleaned for the next user; the reference material is then transferred to an appropriately sized volumetric flask and the standard solution prepared.
- The balance prints a label for the reference solution containing all quality and regulatory information, supporting the audit trail and removing the need for manual transcription of the results.
- The analyst inputs the actual weight of the reference substance into the spreadsheet software, together with any correction factors such as purity or salt to base conversion, and automatically calculates the concentration of the reference standard solution. The spreadsheet is then printed out and the analyst pastes the balance and spreadsheet printouts into the lab notebook.
- The analyst checks the data and results. This check is more complete than for the manual process as all data is available on the two printouts. The calculation need not be repeated or verified as the spreadsheet is validated; once the data checks show the data is correct, the analyst can sign the relevant pages of the lab notebook.

Manual Process with a Printer

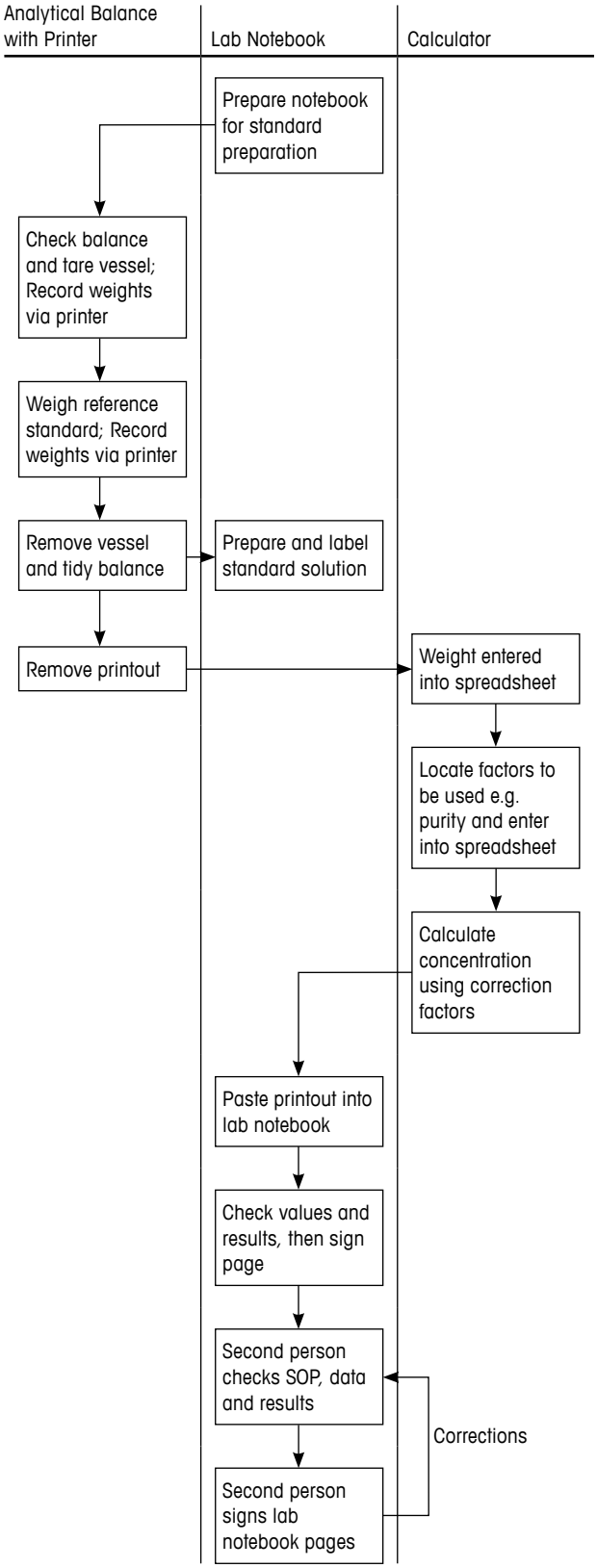


Figure 4: Cross-functional process workflow for an analytical balance with printer attached.

In this scenario, second person review becomes more relevant, as there is now a complete data trail to follow. The data trail demonstrates that the SOP was properly carried out and the data generated is correct. The reviewer can sign the lab notebook without needing to perform any manual calculations.

2.4.1.1. Process Improvements

As seen in Figure 4, a number of improvements are apparent in the new process relative to the manual workflow outlined in Figure 3:

Data Integrity: The integrity of the data generated in this process has improved: the original weighing results are available on the balance printout together with some metadata, including the date/time that the operation was performed and the name of the analyst.

Paper Audit Trail: As a consequence of improved data integrity the audit trail is complete, as the original results can be traced from the balance printout to the spreadsheet for calculation of the standard concentration.

Error Reduction: Transcription errors from the balance and calculator have been eliminated by incorporation of the balance printer.

Improved Process Speed: Manual calculations by the analyst and the reviewer have been eliminated, with the spreadsheet accelerating this part of the process. Second person review of the data is quicker and more meaningful owing to the complete data audit trail.

2.4.1.2. Process Meets Regulatory Expectations

Use of a printer improves weighing data quality and establishes an audit trail from the weighing of the reference standard to the calculation of solution concentration. This allows a regulated laboratory to meet GLP/GMP expectations [Ref 1, 2] and reduces the likelihood of warning letters, as shown in the previous section.

Disadvantages of the Process
Despite the improvements there are still parts of the process where errors can occur, and further optimization is possible.

Manual Data Entry in Spreadsheet Software: Transcription error checking is not eliminated as the balance result and any conversion factors must be entered into the spreadsheet. These figures must be checked by the analyst and the reviewer to ensure that they are correct.

Paper Based Process: As Figure 4 makes apparent, the process is paper based. Two printouts are produced and are pasted into the laboratory notebook to form the analytical record. This, together with the preparation and summary of the work that needs to be written by the analyst, results in a slow process.

Further improvement of the process, and elimination of the transcription check, can be achieved by working electronically, as detailed in the following section.

2.4.2. Process 3: Weighing Using LabX Software

A completely electronic process can be realized with METTLER TOLEDO's LabX software, which can replace the lab notebook, the spreadsheet software and the associated printouts previously described. LabX has the technical controls to support data integrity in compliance with GLP/GMP regulations for electronic records and electronic signatures. [Ref 3, 4]

A function of more importance to regulated and non-regulated laboratories alike is the ability to sign records electronically. While a non-regulated laboratory need not comply with pharmaceutical industry regulations, cost-consciousness, assay standardization and improvements to productivity remain relevant topics everywhere, and this is where LabX software can help.

Implementing LabX allows an analytical process to be made fully electronic. It eliminates sources of transcription error, improves data integrity and quality, speeds up the overall process, and reduces the time needed to perform a task.

LabX is a configurable software application; the SOP for preparing a standard solution can be incorporated into an electronic workflow and validated, enforcing compliance with the written procedure.

- The LabX electronic process starts with the analyst selecting the reference standard to weigh and then logging onto LabX at the terminal of the analytical balance. There is no need to log onto a separate workstation to access LabX.
- Balance checks must be performed if prompted by LabX. Otherwise the analyst tares the weighing vessel, then weighs the reference material.
- No results need be recorded by the analyst, as LabX does all the work: actions and weights are stored in the database against the user's identity, together with a timestamp.
- Dissolution of the reference material in the volumetric flask and dilution to the appropriate volume are carried out by the analyst.
- A printer attached to LabX can produce a label containing the requisite quality or regulatory information, including the sample identity, concentration, expiry date, etc., for the volumetric flask.

Electronic Weighing Process

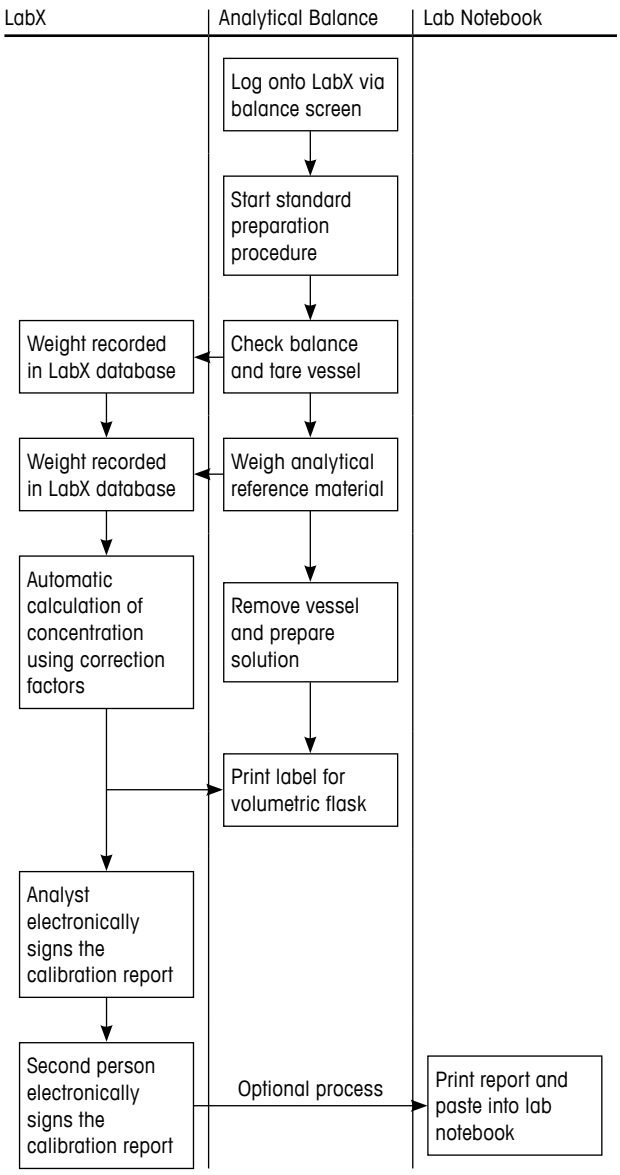


Figure 5: Cross-functional process workflow for an analytical balance connected to LabX software.

When complete, process validation simply requires that the analyst electronically sign what has been done. The electronic system also greatly simplifies the reviewer's tasks: as the process is enforced by the software, no secondary checks for transcription or calculation errors are required. The process and records are held within a single system and need not be re-assessed; once the data is checked by the reviewer the records can be electronically signed.

LabX includes the option of printing out the record, although this is not strictly necessary unless required by local procedures or practices.

2.4.2.1. Advantages of the Electronic Process

There are a number of advantages to the electronic process shown in Figure 5:

- **Elimination of Manual Data Entry:** There is no manual data entry in the process; all data is captured via LabX and securely stored on the server.
- **Elimination of Transcription Errors:** All transcription errors have been eliminated, which was not possible with the processes detailed above. In the single process controlled by LabX, manual data-transcription is no longer necessary and the analyst can focus on scientific work rather than clerical tasks.
- **Single System Log-On:** Interfacing an analytical balance to LabX turns its display screen into a terminal for interaction with the software. A user logs onto the system via the balance screen rather than at a separate workstation; no separate terminal is necessary for operating LabX.
- **Fast, Efficient Process:** The electronic process is faster than an analogous paper-based one, saving laboratory time and effort.

Barcoding to Further Reduce Manual Data Entry

METTLER TOLEDO's new P-58 printer is capable of printing various symbology barcoded labels (e.g. with code 128, QR codes, etc.) that can be affixed to containers of analytical reference substances to identify them uniquely. Balances with a barcode reader can scan these labels and automatically input the identity of the compound, thus avoiding manual data entry as well as accelerating process execution. Laboratories may wish to consider barcoding a range of commonly used samples to prevent errors from occurring.

2.5. Comparison and Summary of the Three Ways of Working

Table 7 shows a comparison of activities performed in the three workflows outlined above, as well as the time taken to perform each one. This illustrates the benefits of process optimization by use of either a balance printer or LabX to reduce errors and ensure data integrity.

Activity Performed	1. Manual, no Printer	2. Manual, with Printer	3. Electronic, with LabX
Prepare lab notebook for work	•	•	–
Log on via balance screen	–	–	•
Check balance function and tare vessel	•	•	•
Document check in lab notebook	•	–	–
Weigh reference standard	•	•	•
Record value in lab notebook	•	–	–
Remove vessel and tidy balance	•	•	•
Paste printout into lab notebook	–	•	–
Calculate concentration manually	•	–	–
Enter values into spreadsheet	–	•	–
Calculate results in spreadsheet and print	–	•	–
Paste spreadsheet printout into lab notebook	–	•	–
Check work; analyst signs lab notebook	•	•	–
Second person checks work	•	•	–
Correction of any mistakes	•	•	–
Second person signs lab notebook	•	•	–
Automatic calculation of results	–	–	•
Analyst electronically signs report	–	–	•
Second person checks work	–	–	•
Second person electronically signs report	–	–	•
*** Overall Time for the Process**	**25 min.**	**20 min.**	**8.5 min.**

Note: * Verified in internal lab tests.

Table 7: Comparison of time expenditure for manual, semi-automated and automated record-keeping processes.

As can be seen in Table 7, substantial time-savings can be achieved by moving away from a purely manual process.

What do these figures mean in practice? As weighing is a very common activity, let us examine the implications for a relatively small laboratory with a staff of 10 analysts.

If each analyst performs 1,000 weighing operations per year (reference standards, samples, control samples and preparation of buffers and mobile phases), which translates to four to five per working day, there will be a cumulative total of 10,000 weighings per annum in the laboratory. Using the timing figures from Table 7, we can calculate the total time spent on weighing operations in this laboratory (Table 8).

The first row of Table 8 outlines the total time spent on weighing in the laboratory; it is calculated by multiplying the time for the operation from Table 7, converting this to days and dividing by 220 working days per year. The result of the calculation is expressed as Full Time Equivalents or FTE. This was chosen as the unit of measurement because any laboratory in any country will understand the amount of time considered and the savings that result.

	1. Manual, no Printer	2. Manual, with Printer	3. Electronic, with LabX
Total time spent on laboratory weighing	0.79 FTE	0.63 FTE	0.27 FTE
Saving with changed process (per annum)	0	0.16 FTE	0.52 FTE
Percentage process improvement over baseline process	Baseline	25%	–
	Baseline	–	194%
	–	Baseline	134%

Table 8: Improvements in efficiency over baseline (manual) time expenditure with automation solutions.

As can be seen in the table, while small improvements can be made with the addition of a printer, the greatest productivity gain is achieved when moving to an electronic process. In our example, the electronic process can save working time equivalent to half a person per year on an ongoing basis when compared to a manual process without a printer. These gains are in addition to the reduction in errors already discussed.

Here we have investigated productivity gains and time improvements in a relatively small laboratory. For larger laboratories with more personnel, or where more weighing tasks per analyst are performed, the time and productivity savings will increase.

For GxP-regulated laboratories, there is always the need to validate the software before use (see section 1.8). The cost of validation needs to be factored into the overall cost and payoff calculations.

1. Manual, with Handheld Calculator Only	2. Manual, with Printer and Spreadsheet	3. Electronic, with LabX and Electronic Signatures
• Transcription of results from balance screen to lab notebook subject to error • No independent check of balance readings • Approach not accepted by GxP inspectors as no independent evidence of weight taken • Manual transfer to spreadsheet • Two manual transfers of data followed by two checks for transcription error • Slowest and most error-prone process	• Printout of weighing results and ability to review data from start to finish • Elimination of one round of data transcription and associated checks • Improved data integrity • Validated spreadsheet • Approach acceptable to GxP inspectors • Faster than Process 1; reduced errors due to printouts	• Fully electronic process • Validated software and process • Automated data capture—no manual data transcription required • No transcription checks required • Printout of final signed report optional • Fastest process of the three examples

Table 9: Comparison of error reduction, quality improvement and data integrity among manual, semi-automated and automated processes.

Table 9 compares the error reduction and quality improvement from the manual process to the electronic process using LabX. One of the key points expressed by the table is a reduction in laboratory error.

Yet laboratory error depends heavily on context. To investigate further, we can compare studies that have looked at error rates in laboratories. Although data from analytical laboratories is not readily obtainable, clinical chemistry laboratories offer insight. Clinical chemistry involves the analysis of patient samples, including human blood, urine and tissues, to assist in the diagnosis and management of diseases. Mistakes in this area can critically impact the health of a patient, so reducing errors is essential.

- One paper, entitled "The Blunder Rate in Clinical Chemistry", measured the analytical errors detected before and after the introduction of a LIMS. Incidence of errors was reduced from about 5% to less than 0.3% after implementation of computerized data management. [Ref 7]
- Manual transcription errors in patient blood results recorded in a critical care setting by comparing handwritten and printed laboratory results for 100 consecutive patients in the intensive care unit of a UK hospital. Out of 4,664 individual values, 67.6% were complete and accurate, 23.6% were not transcribed at all, and 8.8% were inaccurate transcriptions of the results. Interestingly, this study found that the most accurate work was performed in the morning. [Ref 8]

The first study shows that the overall impact of automating a process results in a 10-fold reduction in input errors to a LIMS. The second shows that when personnel are under pressure, as in an intensive care facility, the error rate increases. Therefore, in a laboratory with a manual process, diligent performance of secondary checks is likely crucial to ensuring that as many errors as possible are caught and corrected.

By inference, use of an instrument control software application such as LabX to automate weighing processes, as described earlier, should also prevent many data input errors.

2.6. Validation of an Electronic Process

Software used in GxP-regulated laboratories must be validated for its intended use. Guidance documents such as the GAMP version 5 guidelines [Ref 5] and the GAMP Good Practice Guide, entitled "A Risk-based Approach to Compliant Laboratory Computerized Systems" [Ref 6], are available. However, in regulated laboratories there is often a fear that computer validation will be a slow, laborious, burdensome and paper-based process.

If a risk-based approach to validation is taken, these fears will not be realized. Validation of LabX can use a simpler life cycle for configurable software, and most of the testing effort should be focused on the configured process rather than the basic application. The effort of validating software should be considered in context with the daily savings gained by use of the software throughout the laboratory. The principle of "validate once and use multiple times" holds here.

Furthermore, computer systems validation should be viewed as a benefit rather than a cost. The time savings owing to use of a validated electronic process far outweigh the one-time cost of validating the application. The time saved increases the duration of time in which personnel can focus on more productive tasks in the laboratory.

A realistic estimate of the time required to validate a LabX system is between 20 and 40 days. However, this time encompasses the whole system, which may include a number of instruments, each with a range of associated processes. If we assume that LabX will only be used to weigh reference substances and prepare solutions as outlined in Process 3, even in the worst case of 40 days to complete the validation of a single process, this equates to 0.18 FTE. The time saved by using an electronic process as calculated in Table 8 is 0.27 FTE. This means that in the first year, the laboratory still saves at least 0.09 FTE, and 0.27 FTE per year thereafter. If the computer system validation is quicker, the savings obtained will be greater. As noted above, the calculations included here are for a small laboratory; for a larger laboratory the savings will be relatively greater, with the same validation costs.

3. An Example for Simultaneous Measurement of Density, Refractive Index, pH and Color

3.1. Multiple Analyses Required for Quality Control

Complex products that comprise a multitude of raw materials, including flavorings and fragrances, need highly accurate analyses to monitor production processes and final products alike. Quality control requires the processing of many samples in a short time; each must be checked to ensure that it falls within the corresponding limits, and often also retained for reference; and results must be logged, analyzed and reported, without transcription errors.

Where multiple parameters must be measured, analyses may be time-consuming; yet special care must also be taken to avoid sample alteration between single analyses.

A multiparameter system permits the improvement of an analytical workflow by enabling the automatic QC analysis of up to four different parameters (typically density, refractive index, color and pH). Running all these analyses with a single, combined system helps to save time and increase throughput. As all analyses are performed simultaneously, sample alteration is not a concern. Samples can also be pushed back to their vials after measurements for retention as references.

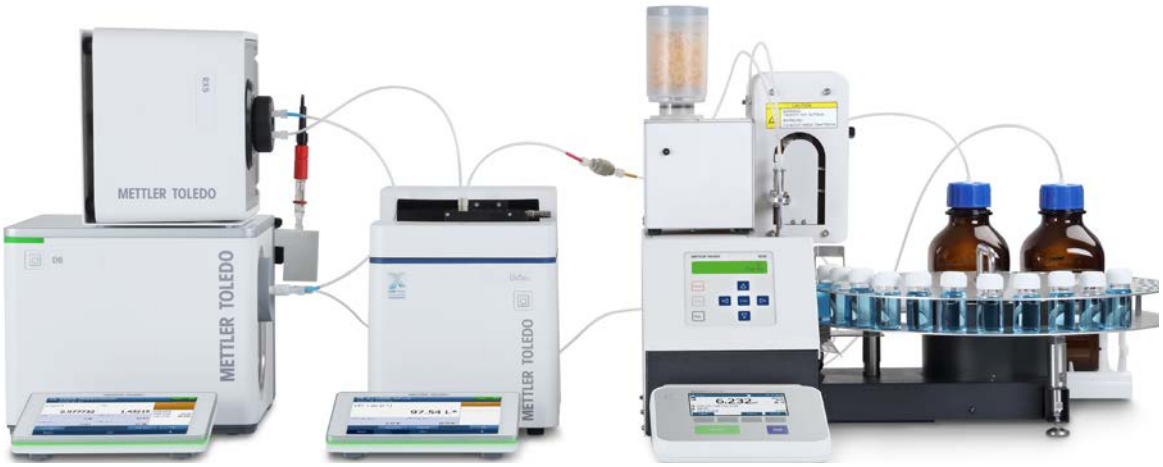


Figure 6: From left to right: density meter, refractometer cell, pH electrode, UV/VIS spectrophotometer, pH meter, SC30 sample changer.

- The workflow begins with preparation and labeling of vials containing samples of incoming goods, products in preparation, or final products. These are loaded onto an SC30 multiple sample automation unit; if desired, a manual barcode scanner, or a barcode scanner built into the SC30 automation unit, can be incorporated to improve sample tracking and data integrity.
- From there, the operator launches the method by pressing a shortcut on the screen of an Excellence density meter. An aliquot of each sample is pumped into the flow cells of all instruments implicated in the multiparameter analysis (see Figure 6); once sample filling has completed, the analyses are started simultaneously, ensuring that sample alteration over time (e.g. due to evaporation) need not be considered. Samples are automatically discarded or pushed back to their vials for retention, depending on the SOP; the flow cell is then cleaned and dried for measurement of the next sample.
- Once each analysis has completed, results are compared against reference values looked up by LabX in a connected LIMS; pass/fail information is displayed on the screen of both the density meter and the PC, enabling quick detection of, and reaction to, any problems with materials or formulated products. The data is simultaneously stored in LabX's database and backed up in the LIMS, if applicable, supporting compliance.

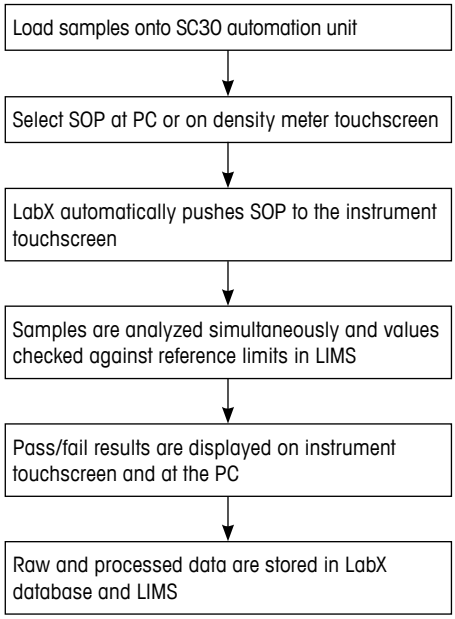


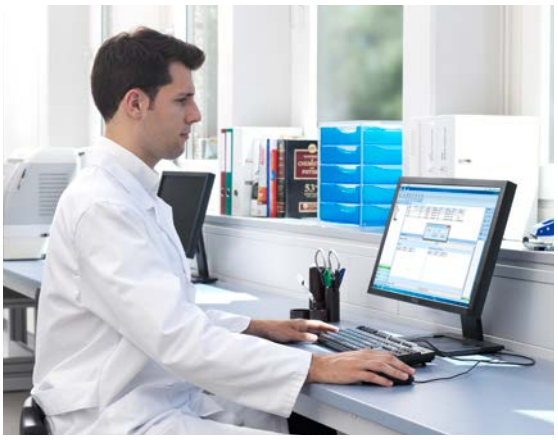
Figure 7: Process for automated multiparameter measurement controlled by LabX.

A short video of a multiparameter system in operation is available here.

In contrast, a fully manual process employing all four instruments would require the operator to load samples sequentially into each instrument, take a measurement, record data, and then clean and dry the instruments; it would also require manual calculations and lookup of reference control limits to determine pass/fail status. Not only does each measurement require more time, but sample processing is also slowed considerably. Samples may alter due to environmental or other influences between assessments on the first and any of the subsequent instruments; manual data-transcription, calculations and lookup for comparison to reference samples all pose the risk of errors; and the longer process may inadvertently lead to waste, in the event that sample measurements are found to exceed control limits after production has been underway for some time.

3.2. Seamless Connection to LIMS, SAP or ERP

Bi-directional integration of LabX into a company's IT system can be of substantial benefit when many reference materials are implicated. As indicated above, SOPs are pushed directly from the LabX software to all instruments with no need for additional input; complete user guidance allows a technician to work either at the instrument or at the PC, based on the SOP. Results of all measurements are shown on the instrument following completion, and are transferred both to LabX's central database and the LIMS. In addition, detailed evaluation of all analyses can be performed on the lab manager's PC either immediately or at a later date.



3.3. Benefits

A multiparameter system consisting of Excellence series instruments driven by LabX allows the measurement of up to 30 samples with One Click™ with the inclusion of an SC30 multiple sample automation unit. No operator interaction is required after sample loading, saving considerable labor time (up to 70%) and increasing throughput (up to 50%). As the measurements are performed automatically, using identical conditions, operator influence is removed, resulting in higher data accuracy. Moreover, simultaneous sample analyses in closed measuring cells minimizes the likelihood of sample alteration due to elapsed time or evaporation.

With SOPs displayed directly on the instrument screen, paperless operation is possible. Automatic capture of complete data in LabX prevents transcription errors and provides an immediate overview of results, enabling quick action in case problems are spotted. In addition, changes in the product database will be mirrored immediately in LabX for seamless analysis of further products. Instruments such as a titrator or polarimeter can also easily be added to assess further parameters.

4. An Example for Titration

Weighing samples is an integral part of almost any titration application. This preparation step bears the risk of transcribing the weights wrongly or getting the sample sequence mixed up.

4.1. Efficient and Error-Free Titration Workflows

Manually recording titration sample weights and IDs can be a laborious and error-prone task, if each sample weight and ID is logged manually into a notebook or written on the sample beaker, then keyed into the titrator. The new SmartSample™ system improves this workflow by automatically transferring sample data from the balance to the titrator using the Smart Tag radio frequency identification (RFID) tag. A Smart Tag can be attached directly to a sample beaker or to a removable sleeve and stores sample ID, weight and other relevant data.

Figure 8: RFID-enabled Smart Tags attach to sample beakers, linking each titration sample's data and metadata to it from the balance to the results.

4.2. Automated Data Transfer

Using the Smart Scan accessory for METTLER TOLEDO Excellence analytical balances is the first step of automated data transfer. Smart Scan allows the editing of entry fields to store all information required, including weight, batch number and product number. The necessary sample data may be specified by SOPs, regulations or legal requests. An additional practical feature of Smart Scan and the Excellence balance software allows automatic incrementing of ID numbers, e.g. 123, 124, 125, etc.

The second step of automated data transfer is the reading of a Smart Tag by the InMotion™ sample changer. After a titration is started, all sample data is transferred from the RFID tag on a sample beaker to the titrator, and utilized in the analysis and presentation of results.

Sample information need only be recorded once before its automatic and unambiguous transfer. With no manual data-recording or -entry required, valuable time is saved on each sample and transfer errors are prevented.

4.3. Automatic Method Selection with LabX SmartCodes

Samples can be placed on the InMotion sample changer in any order, with SmartSample ensuring appropriate sample tracking. However, each sample needs a titration method to be assigned for proper analysis.

Method selection can be fully automated using SmartCodes™, a functionality of LabX laboratory software that allows the automatic assignment of a particular titration method to every sample, to bring workflow security and automation to the next level. Based on data stored on the RFID tag, LabX automatically selects the correct method, which is then executed for the respective sample. In this way:

- The right method is always activated;
- Any number of samples can be accepted without specification of a defined number in advance; and
- Unplanned samples can be measured at any time between other samples.

The InMotion Autosampler rack can be filled with samples requiring different titration methods. The entire set of samples can be analyzed with One Click on the titrator's touchscreen.

SmartCodes can be defined in LabX software. The editor requests the following entries:

- Name of Smart Code, e.g. Acidity 65
- Sample correlation, e.g. sample ID, product ID, etc.
- Method correlation, e.g. method ID (number)

Figure 9: The SmartCodes function of LabX permits users to link titration methods directly to samples, such that sequential samples need not be analyzed using the same protocol.

4.4. New Level of Data Integrity

SmartSample prevents manual errors due to incorrect data transcription or sample mix-up, while SmartCodes enable the titrator to identify the appropriate method and perform the right analysis without fail. In combination, these measures render workflows doubly secure, supporting data integrity.

5. Summary

Directly connecting laboratory balances and instruments to laboratory information systems offers significant advantages. Yet implementation often suffers from technical limitations and cost overruns, with less than desirable results. LabX software incorporates laboratory balances and analytical instruments into a single "benchtop environment" at the IT foundation level, offering significant advantages and efficiencies compared to other approaches.

Integrating LabX instrument control software with other laboratory information systems using .csv files, XML structure or APIs closes the gap in traceability, simplicity, total cost of ownership (TCO) and cost/time efficiency. Any system that can handle .csv, .xml or web services can integrate directly with LabX and, in turn, its connected instruments. The lab can benefit from the complementary advantages offered by benchtop instruments, instrument control software and laboratory information systems working together, each doing what it is designed to do, with minimal overhead.

By installing LabX software, organizations wishing to improve weighing and analytical results, quality compliance, data integrity and efficiency through automation can take advantage of the instrument technology that in many cases already resides on the benchtop. LabX offers an easy-to-use, transparent user experience that uniquely addresses many challenges of the user organization.

METTLER TOLEDO provides full support services for easy start-up and can assist with guidance on establishing and maintaining effective quality management programs to complement a LabX installation.

6. References

Reference used in the creation of this guide follow.

[1] FDA Guide to Inspections of Pharmaceutical Quality Control Laboratories (1993), section 13

[2] FDA Guide to Inspections of Pharmaceutical Quality Control Laboratories (1993), section 14

[3] Electronic Records; Electronic Signatures Final Rule, 21 CFR 11

[4] EU Good Manufacturing Practice regulations, Annex 11, "Computerised Systems"

[5] Good Automated Manufacturing Practice (GAMP) Guide, Version 5, International Society for Pharmaceutical Engineering, Tampa, Florida (2005)

[6] GAMP Good Practice Guide, A Risk-based Approach to Compliant Laboratory Computerized Systems, International Society for Pharmaceutical Engineering, Tampa, Florida (2012)

[7] A.M. Chambers, J. Elder and D. StJ. O'Reilly, Annals Clinical Biochemistry, 23 (1986) 470–473

[8] R. Black, P. Woolman and J. Kinsella, Presented at American Society of Anaesthesiologists Annual Meeting, New Orleans, Louisiana, October 2001

[9] Current Good Manufacturing Practice for Finished Pharmaceutical Products 21 CFR 211.68(b)

LabX Software Solutions

For Data and Workflow Management

The LabX® software provides a complete, traceable record of results captured on METTLER TOLEDO Excellence series instruments. Linking instruments together to gather data in parallel or in sequence, it deploys fully automated experimental workflows managed in a common interface.

- **Customized Set-Up:** Easily define or configure SOP-compliant methods, and user permissions, for each instrument connected
- **Error-Free Protocols:** Launch workflows involving one or more instruments from a PC or instrument. Prompts on the instrument touchscreen ensure that operators follow methods precisely
- **Secure Data-Management:** Manual alterations to results are logged and tagged to indicate who changed them and why, for compliance with 21 CFR Part 11

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