White Paper

Weighing Data Integrity

3 Ways to Ensure Compliance

Ensuring the reliability and integrity of data generated across the entire pharma production chain is fundamental to regulatory compliance around the world. Also weighing processes – particularly quality critical ones – need to follow those principles. Moving from paper-based systems to hybrid paper-electronic systems or fully automated, networked data-capture can help reduce documentation errors and optimize processes.

Weighing – though sometimes oversimplified or neglected – is an important process step in pharmaceutical manufacturing. Dispensing raw materials, dosing material into a tablet coater, checking granulation or tableting all require weighing and documentation for complete, compliant batch records. As such, Good Documentation Principles apply to these activities as stated in relevant Good Manufacturing Practice (GMP) guidelines.

Automating all or a part of this data gathering with electronic solutions can help make sure documentation is accurate, traceable and stored safely. In this paper, we will compare manual transcription to documentation with three automated or partially automated solutions, assessing the pros and cons of each.

Table of Contents

METTLER TOLEDO

Regulations & Definitions

The reliability and integrity of pharmaceutical data is fundamental to regulatory compliance and patient safety. Having confidence in generated data and being able to reconstruct production activities are key. All major regulatory agencies are currently focusing their activities in terms of inspections and publications on the topic of data integrity. Under this close scrutiny, many pharmaceutical companies worldwide have been warned by inspectors because they allegedly falsified or altered data, or because they failed to keep accurate information trails about how they produced or tested their drugs.

When analyzing warning letters issued by the FDA between 2013 and 2015, letters citing data integrity issues have risen significantly, especially outside the US (Figure 1, Reference 1). A similar picture is true for other regulatory authorities.

Number of warning letters citing data integrity

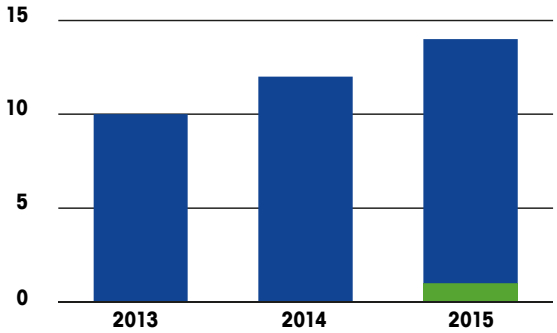


Figure 1: Warning letters that cite data integrity violations in plants in the **US** ■ and **outside US** ■ .

Principles of Data Integrity

Recent guidelines on this topic use similar terms and definitions. What are the most important aspects to consider, and how are common technical terms defined?

- **Data integrity** – Data is complete, consistent and accurate in all paper and electronic forms.
- **ALCOA principle** – Data should be attributable to the person generating it, legible and permanent, contemporaneous, the original record or a true copy and accurate. Recently ALCOA+ has been introduced that adds the following attributes: complete, consistent, enduring and available.
- **Data criticality** – Defining how important data is to quality, safety and efficacy decisions, determined by considering the type of decisions influenced by the data.
- **Data risk** – Reflecting the vulnerability of particular data to unauthorized deletion or amendment and the opportunity to detect such alterations during a routine review.
- **Raw data** – Original records retained in the format in which they were generated (paper or electronic) or a true copy. Raw data must permit the full reconstruction of activities that generated the data. In the case of basic electronic equipment which does not store electronic data or only provides printed output, the printout constitutes the raw data.
- **True copy** – Copy of an original recording of data that has been verified and certified to confirm it is an exact and complete copy that preserves the entire content and meaning of the original record.
- **Metadata** – Data that describes the attributes of other data and provides context and meaning. These are data that describe structure, data elements, interrelationships and other data characteristics. It also permits data to be attributed to an individual or to the original data source. Metadata forms an integral part of the original record.
- **Audit trails** – Metadata that are a record of critical information and that permit the reconstruction of activities. Computerized systems should always provide for the retention of audit trails to show all changes to the data while retaining previous and original data. It should be possible to associate all changes to data with the person making the changes.
- **System user access** – The use of access controls to ensure that people have access only to functionality that is appropriate for their job role and actions taken are attributable to a specific individual.

References 2, 3, 4

Weighing Data Management and Solutions

Manual recordkeeping and transcription is still a popular way of documenting weighing data. It is also one of the major sources of error and other data integrity violations. Mixing up numbers, leaving out important information or not recording values in the proper forms are examples of trouble spots. In severe cases, data is backdated or even fabricated. Not keeping raw data and not documenting routine testing or calibration data are other examples.

Lack of training and fatigue can cause errors such as these to occur more frequently in cases where documentation is manual. Manual recordkeeping is also time consuming and keeps operators from performing other value-added activities. If the 4-eye-principle applies, additional personnel must check to see if data has been captured accurately, adding to the time required and potentially affecting productivity.

Frequently observed data integrity issues in pharmaceutical manufacturing:

- Not recording activities contemporaneously
- Data backdating
- Data fabrication (falsification)
- Copying existing data as new data
- Re-running samples
- Discarding data
- Not being able to produce raw data

Data Management: A typical weighing process

A typical weighing process requires the following data-management activities (workflow, Figure 2):

- Creating and transferring the recipe or procedure to be followed
- Carrying out the actual weighment
- Transferring the results to the batch record
- Transferring this data to a MES system for analysis and storage

In the pages that follow, we will compare how these actions are handled manually against three potential solutions for improving the accuracy and ease of data transfer during typical weighing processes. Specifically, we will look to see where gains can be made in terms of data accuracy, transfer speed and regulatory

compliance to help pharmaceutical manufacturers avoid warnings and citations while maintaining the productivity required in today's competitive pharmaceutical marketplace.

Figure 2: Weighing process – data acquisition, generation and transfer.

Option 1: Adding a Printer

A basic way to reduce transcription errors is to use the print capabilities of your balance or scale. Adding a printer is a simple way to document and store data.

An example data flow (Figure 3) at a weighing station used to capture tablet weights after coating might look like this:

1. Results generated by the scale are printed on paper. Some metadata maintained in the instrument can be added.
2. Printed records are then used to manually transcribe figures into reports.
3. Reports are checked for errors by a second person following the "4 eyes" principle.
4. Data may also be manually transcribed into an ERP system.

Data integrity Checklist

Traceability ensured	✔
Low risk of transcription errors	✔
Efficiency of process	✔
Transfer of metadata	✔
Audit trail (system & data)	✖
Centralized data storage	✖
Paperless production	✖
Electronic signatures	✖
FDA 21 CFR Part 11 / EU Annex 11 compliant	✖

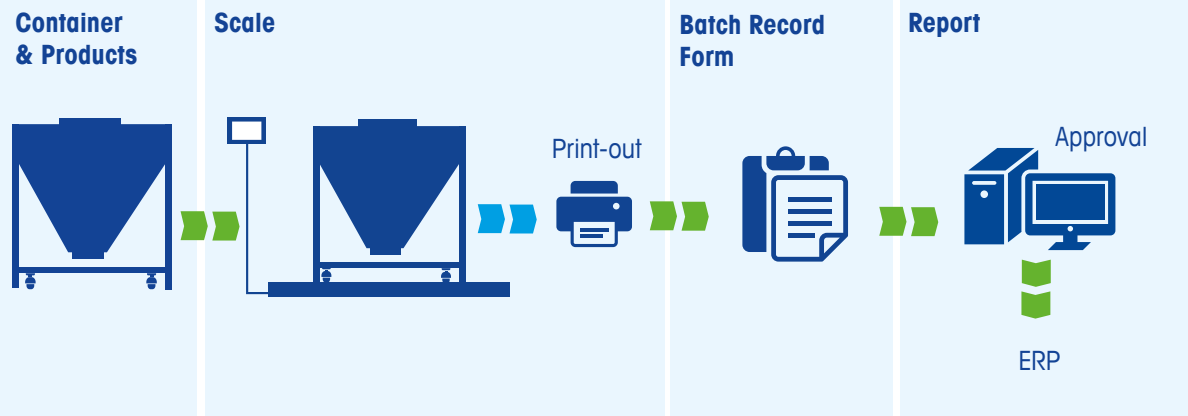


Figure 3: Data flow with weighing results documentation and storage on a printout eliminates one source of transcription error. Additional steps are still manual.

Manual Transfer Automatic Transfer

Printouts

A typical printout contains material name, batch number, date and time, weight value/unit, and operator name or ID. This data is considered raw and needs to be maintained and archived. A label creator e.g. DataBICS software available for our ICS terminals allows the generation of custom labels that meet regulatory requirements that can be applied to containers or placed in records.

Batch No.:	0000000
Product No.:	0000000
Product name:	xxx
Lot No.:	000000000
Net:	000 kg
Tare:	0.00 kg
Gross:	00.00 kg
Operator:	xxx
Date:	00.00.00
Time:	00.00.00

Printing eliminates the error risk inherent when we read and note results off a terminal screen. However, this is still a manually intensive process that requires a significant amount of time and attention.

Pros:
Direct printing is a simple way to document and store measurement data without transcription errors. It is cost-effective and easy to implement in existing processes.

Cons:
Information is not ready for digital processing and analyzing. Manual transcription is still necessary. Printouts also have the tendency to fade over time and can be lost. For critical data, the "four eyes" principle applies, which requires additional resources.

Additional features for enhanced data integrity

Terminal user-management functionalities allow the identification of the person carrying out the weighing task and limits access rights to critical functions as required and checked during data-integrity inspections.

Digital material identification using barcode scanners improves automated identification of containers or raw materials. A RS232 or USB-enabled barcode reader can be connected to weighing equipment for easy data capture. Material ID data can be printed on strips or labels. This allows materials identification and transfer to the scale to recall target weights or user instructions.

Option 2: Automated Data Transfer

To eliminate manual steps and related transcription errors, a scale or balance can be directly connected to a computer allowing unidirectional data collection using a PC program. Data is submitted as a text protocol.

An example data flow at a weighing station used to capture container weight before and after granulation might look like this:

1. Results are generated by the scale, then transferredto a computer with the help of data collection software.
2. This data is then transferred to Excel or printed.
3. Reports are double-checked by a second person following the "4 eyes" principle.
4. After that, data may be manually transcribed into an ERP system.

Data integrity Checklist

Traceability ensured	(✔)
Low risk of transcription errors	(✔)
Efficiency of process	✔
Transfer of metadata	✔
Audit trail (system & data)	✖
Centralized data storage	✖
Paperless production	✖
Electronic signatures	✖
FDA 21 CFR Part 11 / EU Annex 11 compliant	✖

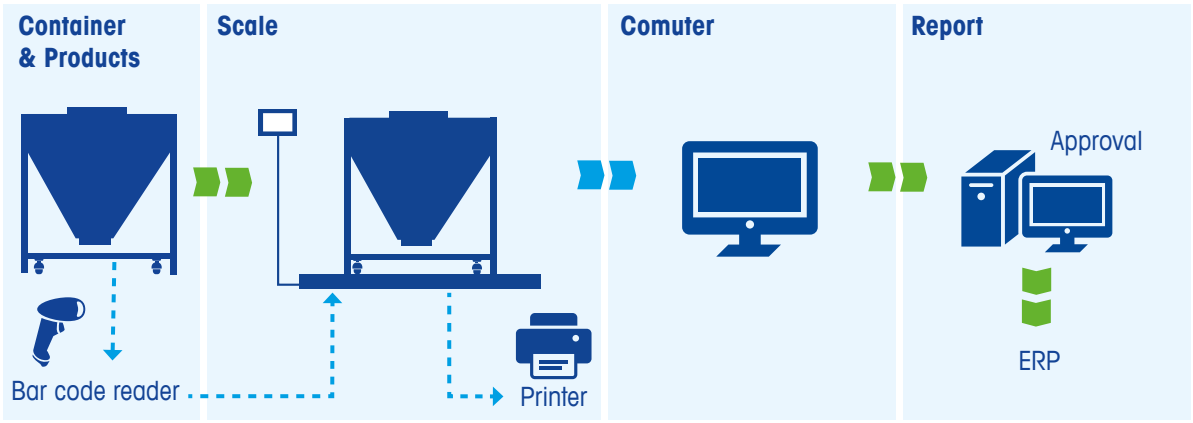


Figure 4: Direct connection or transfer via USB stick. Transcription errors are eliminated and data quality is improved. Additional measures are needed to ensure compliance.

Most common interfaces for data transfer to computer:

Depending on requirements such as data rate and volume, network type, environment/distance from data source or network structure, different scale interfaces are available.

Serial interfaces such as RS232/422/485 or USB allow point-to-point communication between printers and barcode readers or PCs.

Ethernet TCP/IP via cable or WLAN are the most common interface type for PC networks.

Wireless interfaces such as Bluetooth or WLAN allow communication with mobile scales or in locations where cabling is complicated.

Data Communications

Data communication software such as DatabICS or Collect+ allow simple data transfer including some metadata such as value and unit, time and date, material ID, net/gross weight and tare. Layouts are configurable and input masks and calculations are possible.

Further measures such as printing reports, checking data accuracy and obtaining signatures need to be implemented via SOPs. System validation is needed if critical data is processed.

Pros:

Direct transfer from the scale to a computer eliminates manual transcription. Adding simple communication software allows transfer of the value along with part of the metadata. Data transfer is enabled via USB or interfaces such as serial or Ethernet.

Cons:

There is no centralized data storage. Not all metadata is captured and values can still be changed or omitted when reporting without traceability. This lack of an audit trail potentially reduces traceability, making it impossible to find out what data was changed, when and by whom.

Alibi data storage

Many weighing terminals contain a protected internal memory. Originally required by OIML weights and measures regulations, data retained consists of the device serial number, date & time of measurement, net weight and tare. METTLER TOLEDO adds additional data points for expanded data sets. Data cannot be altered in the scale itself. It is provided in CSV format which can be used for further analysis. Data can be retrieved via Ethernet, USB or WLAN depending on scale type.

Option 3: Compliant Networked Solutions

Recipe-weighing software or quality-control software offer strong workflow management as well as data capture and reporting. These software types provide several significant benefits to data accuracy and integrity over simple data-collection software.

For example, at a formulation station where multiple devices are connected and multiple raw materials and recipes are handled, data is highly critical for product quality. Similarly when looking at quality control processes to monitor fill levels or tablet uniformity, weighing or other measurement steps take place at different workstations, calculations need to be carried out and data analyzed in real time to react quickly to product deviations.

In both cases compliant manual documentation processes become resource-intensive. Software can simplify and speed up these processes, capturing savings that offset initial implementation costs.

Data integrity Checklist

Traceability ensured	✔
Low risk of transcription errors	✔
Efficiency of process	✔
Transfer of metadata	✔
Audit trail (system & data)	✔
Centralized data storage	✔
Paperless production	✔
Electronic signatures	✔
FDA 21 CFR Part 11 / EU Annex 11 compliant	✔

- Full traceability: instrument, date, time, method, raw material information and calibration history is recorded. Robust systems include enhanced user-rights management.
- Guided SOPs and automatic data capture reduces waste and rework.
- A complete log and audit: not only is data recorded, but any interaction with the system is logged into the audit trail, telling an auditor or reviewer "who did what, when".
- All data is available for immediate reporting or direct analysis and can be approved by a supervisor.
- All data is stored securely in the database and can be transferred to the ERP system.

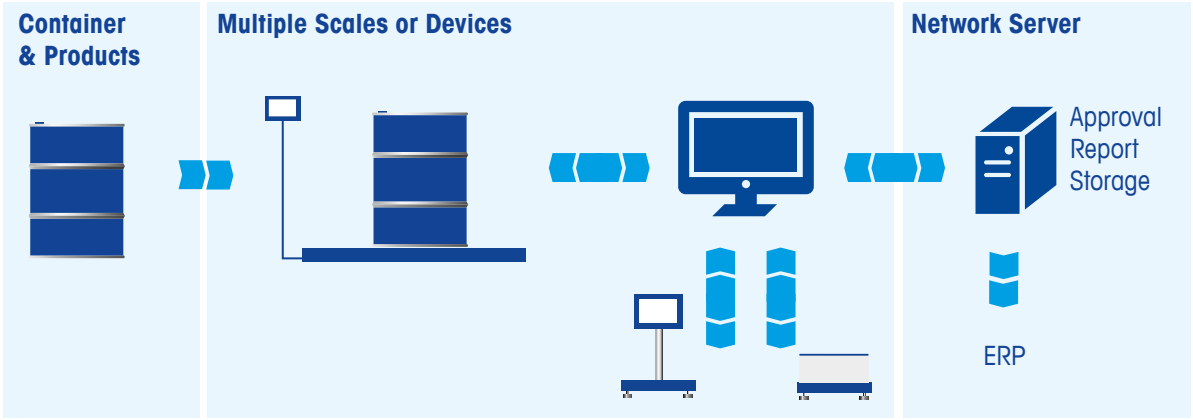


Figure 5: Data flow in digital production with automated transfer of data from the scale to the network server.

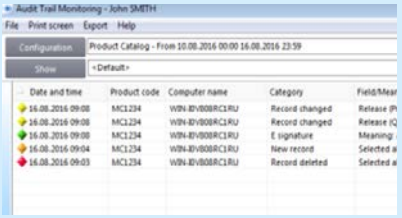
When considering true data integrity in regulated environments, full integration of weighing equipment into compliant software is highly desirable.

Pros:
Data is automatically transferred to eliminate transcription errors and increase productivity. Processes and calculations are guided to ensure each user carries out the same procedures, helping to eliminate rework and waste. Metadata is linked to results, supporting full traceability. A variety of import or export options allow data transfer into existing networks, data archives or ERP systems.

Cons:
Complete solutions such as FormWeigh.Net or FreeWeigh.Net cost more than paper records or direct-to-PC solutions at the outset. However, initial expense is usually made up quickly by error reduction, time savings and traceability improvements.

Figure 6: Statistical quality control software such as FreeWeigh.Net integrates data capture and analysis for many devices including checkweighers and analytical instruments.

Audit trail functionality
The audit trail in FreeWeigh.Net or FormWeigh.Net records all changes to data records, indicating the change itself along with user information and date and time in full compliance with 21 CFR Part 11. The audit trail thus ensures that all changes made to the system can be traced. Once activated, the audit trail cannot be switched off, eliminating the potential for audit trail tampering or loss.



Summary

Humans are capable of error, even when stakes are high. At the same time, pressure on production costs means resources need to be spent wisely. While paper logs have historically been the norm and tend to be low-cost, automation of results capture and storage can help reduce error risk, enhance productivity and reduce waste or rework for more accurate, compliant processes.

There are three levels of non-manual data capture that production units can take advantage of. Each offers a certain level of security, error mitigation and time savings. Whether you choose to add a printer, connect to a higher-level MES system or provide full integration with a workflow and data management system such as FormWeigh.Net or FreeWeigh.Net, capturing data at the point of origin is the foundation of any data-integrity improvement effort. This timely automated capture avoids transcription errors, captures relevant metadata and frees up operators for other value-added tasks.

Weighing Data Transfer: Solutions Snapshot

	Traditional: Manual data recording	**Option 1: Adding a printer**	**Option 2: Automated data transfer**	**Option 3: Compliant networked solution**
Gateway	Eyes Pen	Printer, Bar code reader	Computer USB stick	Network, software such as FormWeigh.Net, FreeWeigh.Net
Traceability ensured	(✔)	(✔)	(✔)	✔
Low risk of transcription errors	✖	(✔)	(✔)	✔
Efficiency of weighing process	✖	(✔)	✔	✔
Automated transfer of metadata	✖	(✔)	✔	✔
Audit trail (system & data)	✖	✖	✖	✔
Centralized data storage	✖	✖	✖	✔
Paperless production	✖	✖	✖	✔
Electronic signatures	✖	✖	✖	✔
FDA 21 CFR Part 11 / EU Annex 11 compliant	✖	✖	✖	✔

✔: full support; (✔): only partially possible or only reachable with additional measures

References

1. FDA Warning Letter Database
http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm

2. MHRA GMP Data Integrity Definitions and Guidance for Industry, March 2015
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/412735/Data_integrity_definitions_and_guidance_v2.pdf

3. WHO Good Data & Records Management Practice, June 2016
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

4. FDA Draft Guidance "Data Integrity and Compliance with cGMP", April 2016
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm495891.pdf

METTLER TOLEDO Product Information

Industrial Weighing
www.mt.com/industrial
Industrial Terminals
www.mt.com/terminals
Printers:
www.mt.com/printers
ICS Scales
www.mt.com/ics689
DatabICS
www.mt.com/ind-databics
Collect+
www.mt.com/collectplus
FormWeigh.NET
www.mt.com/formweigh
FreeWeigh.Net
www.mt.com/freeweigh

Further Reading

Regulatory Compliance Whitepaper
www.mt.com/ind-pharma-regulations
Data Integration Whitepaper
www.mt.com/ind-data-integration
Ideal Dispensing Station Application Note
www.mt.com/ind-dispensing-station

Mettler-Toledo GmbH
Industrial Division
CH-8606 Nänikon, Switzerland
Phone + 41 44 944 22 11

Local contact: **www.mt.com/contacts**

www.mt.com
For more information