White Paper

Bringing Business and Data Integrity Benefits to an Organization

This white paper compares paper based manual process and automated process of laboratory data handling and shows the benefits of an instrument data system. The return on investment will come from automating chemical analysis, earlier release of products, and compliance cost saving by ensuring data integrity in GMP regulated laboratories. In addition to the benefits of an automated system this paper demonstrates how LabX instrument control software can work with ELN, LES or LIMS systems.

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1. Objective

The objective of this white paper is to demonstrate that an investment in an instrument data system including validation of the application can bring substantial business benefits to both a laboratory and its parent organization.

To achieve this, we will examine the regulatory landscape casting a look inside and beyond the laboratory for some of the business benefits that laboratory automation can bring to an organization:

- Business benefits obtained from automating chemical analyses in GMP regulated labs
- Cash flow benefits following from earlier release of products
- Compliance cost benefits by ensuring data integrity for chemical analyses

We will start our discussion from the last point as it provides a firm foundation for understanding the current regulatory environment as well as the position of regulatory authorities globally.

2. Driver 1: Regulatory Push for Data Integrity

The major current emphasis in regulated GMP laboratories is data integrity. Although data integrity in pharmaceutical laboratories can be traced back to the Barr Laboratories case in the early 1990's, it is the emphasis on data falsification and poor data management practices, beginning 2005 with the Able Laboratories fraud case, that focused regulatory attention on laboratory data from creation to reporting.

There is an implicit expectation, with the FDA and European regulatory authorities, that the pharmaceutical industry keep up to date. This is best illustrated with 21 CFR 211 on Current Good Manufacturing Practices (CGMP) for Finished Pharmaceutical Goods –the key word is "current". The preamble to the 1978 CGMP publication states that the meaning of "current" is that industry should keep up-to-date with new advances where one contributes to drug quality. This portion of the regulation appears to have been overlooked.

The current situation in many GMP laboratories is that many are paper based and working practices have hardly changed over last decades. In fact, the FDA Guide to Inspection of Pharmaceutical Quality Control Laboratories issued in 1993 is still relevant a quarter of a century after publication as many working practices in regulated laboratories have not changed substantially. Many laboratories still work using:

- Manual processes
- Blank forms
- Hybrid systems
- Spreadsheets to perform calculations

The problem is that these approaches do not enhance data integrity and also result in higher second person review and administrative overheads.

2.1 Paper Processes Can be Easily Manipulated or Falsified

The 'MHRA Data integrity guidance for industry' notes that balances should either have a printer attached or have automated data capture [1]. The first thing to note is that under no circumstances may balance weighing be accepted by observation - the data are too critical. There must be independent evidence to corroborate the activity. An analytical balance must at the very least have a printer attached.
However, a printer has the potential to be manipulated, as evidenced by two regulatory citations:

FDA Warning Letter, February 2014 (ucm386678):
Your firm failed to follow and document at the time of performance required laboratory control mechanisms (21 C.F.R. §211.160(a)).

- Our investigators found that laboratory analysts did not document the balance weights at the time of sample weighing. Specifically, sample weights used in calculations were created after the chromatographic runs. The analyst admitted that the sample weights that were represented as raw data from the analysis actually were backdated balance weight printouts produced after the analysis and generated for the notebooks. These sample weights were used to calculate related compounds and impurities used in support of method validations submitted in FDA drug applications.

FDA 483 Observation, December 2016:
On December 2016, we observed the scrap area behind the production area of Buildings X and Y to contain controlled documents that had been discarded:

- A balance printout with drug product B dated 14-Dec-2016. After discussing this finding with your firm, you failed to explain why the balance printout was post-dated by two days and therefore indicating an alternation to dates on balances. Your firm's VP of Operations explained that not all balances are password protected.

As analytical balances are so critical, security must be in place to ensure that there is limited access to the clock to prevent time travel. However, post run fabrication of data can be difficult to detect, especially when spreadsheets are used to calculate reportable results and not a secure instrument data system.

2.2 Master Templates and Blank Forms Must be Controlled with Accountability

Since 2016, there have been increasing regulatory requirements for the control of master templates and blank forms i.e. forms that are used to record data to demonstrate that a procedure has been executed correctly.
The FDA [2], PIC/S [3] and EMA [4] data integrity guidance documents all have stringent requirements for the control of:

- Master templates e.g. uniquely identified, controlled, linked to a procedure, reviewed and approved
- Blank forms e.g. uniquely numbered, printed so that copying is easily identified, blank forms must be allocated to a department or individual and accounted for when work is completed and damaged forms must be kept.

The high regulatory risk of blank forms is exemplified with these cases:

FDA Warning Letter, January 2017 (ucm538068):
Your firm failed to establish an adequate quality control unit with the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging materials, labelling, and drug products (21 CFR 211.22(a)).

- Our investigator observed many copies of uncontrolled blank and partially-completed CGMP forms …without any accountability or oversight of your quality unit.
- For example, a supervisor said he photocopied a blank OOS form and transcribed the information because he had made mistakes in the original document. Although your procedures required correcting mistakes on the original form, he made a new copy of a blank OOS form and rewrote the data.
- Our investigator documented that your employees used paper shredders to destroy critical laboratory and production records without the appropriate controls and procedures.

FDA 483 Observation, January 2017:
Document control procedures are not established.

- Specifically, your firm's QC raw data used within the microbiology and analytical laboratories are accessible electronically by all employees. There are no procedures established to control the issuance, use and reconciliation of laboratory raw data worksheets

2.3 Hybrid Systems are Discouraged

When a computerized system is involved, most computerized systems in analytical laboratories are hybrid: electronic records maintained in the computerized system with signed paper printouts. Under 21 CFR 11 regulations, the signature on the paper must be linked with the applicable electronic records used to generate the report. Hybrid systems are also under increased regulatory scrutiny as synchronizing the paper printouts with electronic records can be difficult. Another issue is that paper printouts can still be classified as raw data and the electronic records either ignored or deleted. Backup of standalone workstations in the laboratory can be a major problem.

Because of these issues, WHO has stated [5]:

- The use of hybrid systems is discouraged
- Where legacy systems are awaiting replacement, mitigating controls should be in place.
- Replacement of hybrid systems should be a priority

To illustrate one of the problems with backup of laboratory data from standalone workstations the following citation is relevant:

FDA Warning Letter, May 2016 (ucm502347):
Failure to exercise sufficient controls over computerized systems to prevent unauthorized access or changes to data, and to provide adequate controls to prevent omission of data.

- Our investigator also noted that your firm copied raw data to a CD …, and then deleted the data from the … system to free space on the hard drive. Files copied to the CD were selected manually; the selection process was not supervised. Without audit trail capabilities or supervised file selection, there was no assurance that all raw data files were copied to the CD before they were permanently deleted from the system.

Similarly, using other media such as a USB stick or external drive would result in a similar citation – data must be backed up automatically using software, preferably via the IT department.

2.4 Spreadsheets Used for GMP Calculations Are High Risk

Many laboratories use spreadsheets such as Excel for calculation of analytical data generated by analytical instruments. Typically data are transcribed from a paper printout, entered into the spreadsheet, where the final calculations are printed out. There are several regulatory compliance issues with this approach:

- The spreadsheet is a hybrid system
- The master template must be validated
- The completed spreadsheet must be saved to a secure location and backed up as it is part of the complete data for the analysis
- The resulting printout must be linked to the saved electronic spreadsheet record

FDA Warning Letter, January 2017 (ucm538068):
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)).

- You stored original data in an "unofficial" and uncontrolled electronic spreadsheet on a shared computer network drive. Your analyst stated that original data was first recorded in this "unofficial" spreadsheet and transcribed later to an "official" form. This spreadsheet showed failing results above the limits you established in your procedure, PCH 035 Visible Particle Determination in use prior to September 1, 2014.

FDA Warning Letter, October 2015 (ucm474013):
Your firm failed to prepare batch production and control records for each batch of drug product that include documentation of the accomplishment of each significant step in the manufacture, processing, packing, or holding of the batch (21 CFR 211.188(b)).

- On August 28, 2014, FDA investigators identified instances of non-contemporaneous documentation of batch production activities. Two uncontrolled Excel spreadsheets were used to record discrepancies and certain in-process drug quality data. This data was initially missing in the batch manufacturing record. Your firm later entered this data into batch records and backdated them.
  For example, according to a March 2, 2013 entry in one spreadsheet, you did not perform ….. testing as required after ..... operations of …… mg batch X. Despite this notation, the associated "In Process Sample Analysis Sheet" documents …. testing results from February 22, 2013.
  Although spreadsheets can be very useful in the laboratory, their misuse can bring serious regulatory consequences.

2.5 How Much Risk is Justifiable?

From practical and regulatory perspectives there is a high compliance overhead and high regulatory risk when continuing to work with paper or hybrid processes.

- To illustrate this point, if blank forms (e.g. papers that show how a procedure should be executed and what data should be recorded) are used in a laboratory they must be controlled stringently. The reason is that they can be photocopied and there is no knowing how many times a procedure has been executed before a passing result has been obtained. As shown in the following citation

FDA Warning Letter, January 2017 (ucm538068),
Citation number 2 states:

- Our investigator observed many copies of uncontrolled blank and partially-completed CGMP forms (e.g., environmental monitoring recordings, OOS forms, water testing sheets, and clean room entry and exit logs) without any accountability or oversight of your quality unit.
  For example, a supervisor said he photocopied a blank OOS form and transcribed the information because he had made mistakes in the original document. Although your procedures required correcting mistakes on the original form, he made a new copy of a blank OOS form and rewrote the data.
  Our investigator documented that your employees used paper shredders to destroy critical laboratory and production records without the appropriate controls and procedures. Shredded documents included High Performance Liquid Chromatography (HPLC) chromatograms and a partially-completed OOS form.

The data integrity guidance documents from the FDA, PIC/S and EMA makes it very clear that if blank paper forms are to be used they must be controlled as follows:

- Master templates need to be authored and approved
- When the master form used to create a copy, each blank form needs to have a unique number and be issued by Quality Assurance
- Copies must be secure from photocopying e.g. secure stamp or printed on paper not available in the laboratory
- There must be a track and trace process to monitor issuance and reconciliation of each blank form. Remember this applies to every blank form in the laboratory.
- Each blank form needs to be traced to a laboratory unit or individual who performs the work
- When work is completed, the location of each form needs to be updated in the track and trace system
- If a form is damaged it must not be destroyed but returned to QA and retained. A new form needs a justification for reissue.

This does not make for efficient and effective laboratory operations. There needs to be a better way of working to improve the way laboratories fulfil their role.

3. Driver 2: Laboratory Business Efficiencies Pull

Here we discuss three processes that can be performed for weighing an analytical reference standard, ensuring the solution is the right pH value for compatibility with the HPLC mobile phase. After preparing the reference standard solution, the standard concentration is entered into a chromatography data system (CDS). The three workflows are:

1. Manual operation of an analytical balance and pH meter and manual transfer of the reference standard concentration into a chromatography data system (CDS) for calculation sample results
2. Automation of the process using Mettler Toledo's LabX instrument data system with automated transfer of the standard concentration to the CDS
3. Automation using of the process with the instruments interfaced to an ELN (similarly LES, LIMS, or other such systems) and with automated transfer of the standard concentration to the CDS

Common features of the three processes are:

- There are written procedures describing the work to be performed.
- There are two analytical balances in the laboratory, a four-place and a five-place balance but only the five-place balance is specified for use in this analytical procedure. For the manual procedure, there is a printer attached to document the work performed.
- Each time the balance is used it must be verified to have been calibrated and checked against acceptance criteria specified in the procedure.
- The external masses are calibrated on an annual basis and are traceable to international standards.
- There is a single pH meter that also has a printer attached for use in the manual workflow.
- As per the GMP regulations, a second person review will be performed

The differences in the three processes are summarized as follows:

- For the manual process, there is a controlled and uniquely numbered blank form for the work. For the sake of simplicity, the request and issue of the form has been omitted from the process flow, however in real terms, the time taken for its issue must be factored in to any efficiency calculations. Printouts from the balance and the pH meter are attached to this form and any associated analytical information (metadata) written down by the analyst when performing the work.
- The first electronic process uses LabX software from Mettler Toledo; this is an integrated instrument data system that links multiple instruments in a single analytical workflow. The instruments have touch screen front panels that act as terminals for LabX , removing the need for a PC workstation to control the workflow and collection of data from an instrument. Any calculations performed are defined and validated as part of the workflow.
- The process with the Laboratory Execution System is automated with the instruments connected to the LES and integrated into the workflow. However, it requires a PC in the laboratory because, unlike the LabX option, the balance, pH meter or other instruments cannot be used as terminals. Calculations are specified and validated as with the LabX option but the main difference is that instead of a single integrated workflow, there are two workflows and the result from the weighing needs to be found in the ELN and brought into the pH workflow.

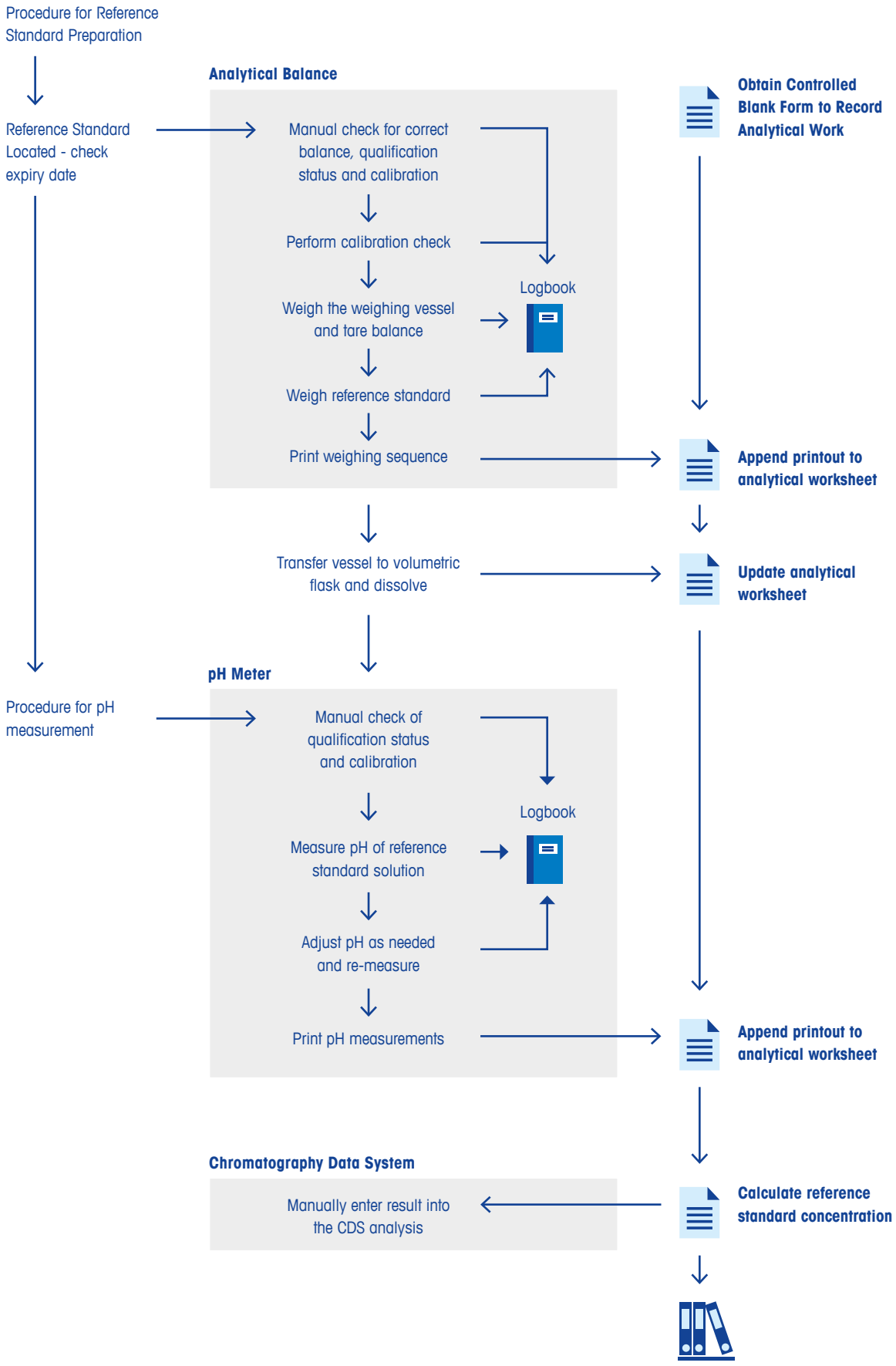

Figure 1: Process Flow for a Manual Process Involving an Analytical Balance and pH Meter

3.1 Manual Process Workflow

The process flow involving the analytical balance and the pH meter is shown in Figure 1.

As you can see from Figure 1, the process is:

- Time consuming
- Completely manual
- Prone to transcription errors when recording data by indelible pen
- Subject to errors occurring in calculations performed with a calculator. These need to be checked by a second person.
- Slow due to checks of the qualification status of instruments, as all information must be checked manually
- Cumbersome as it uses controlled forms to record work that must be formally issued, tracked and reconciled after completion of the analysis

In addition, the workflow has some high-risk data integrity issues:

- How many times has the work been carried out?
- Entering data into a computer system manually is error prone

The second person reviewer must also check:

- The correct analytical balance was used for the weighing
- All fields in the blank form have been completed correctly, there are no missing areas, blank spaces and any corrections have been initialed, dated and a reason for change given
- The calculation of the analyte concentration must be checked, if a calculator has been used
- The manual input of the concentration to the CDS must be checked in the review as this is manually entered critical data according to EU GMP Annex 11

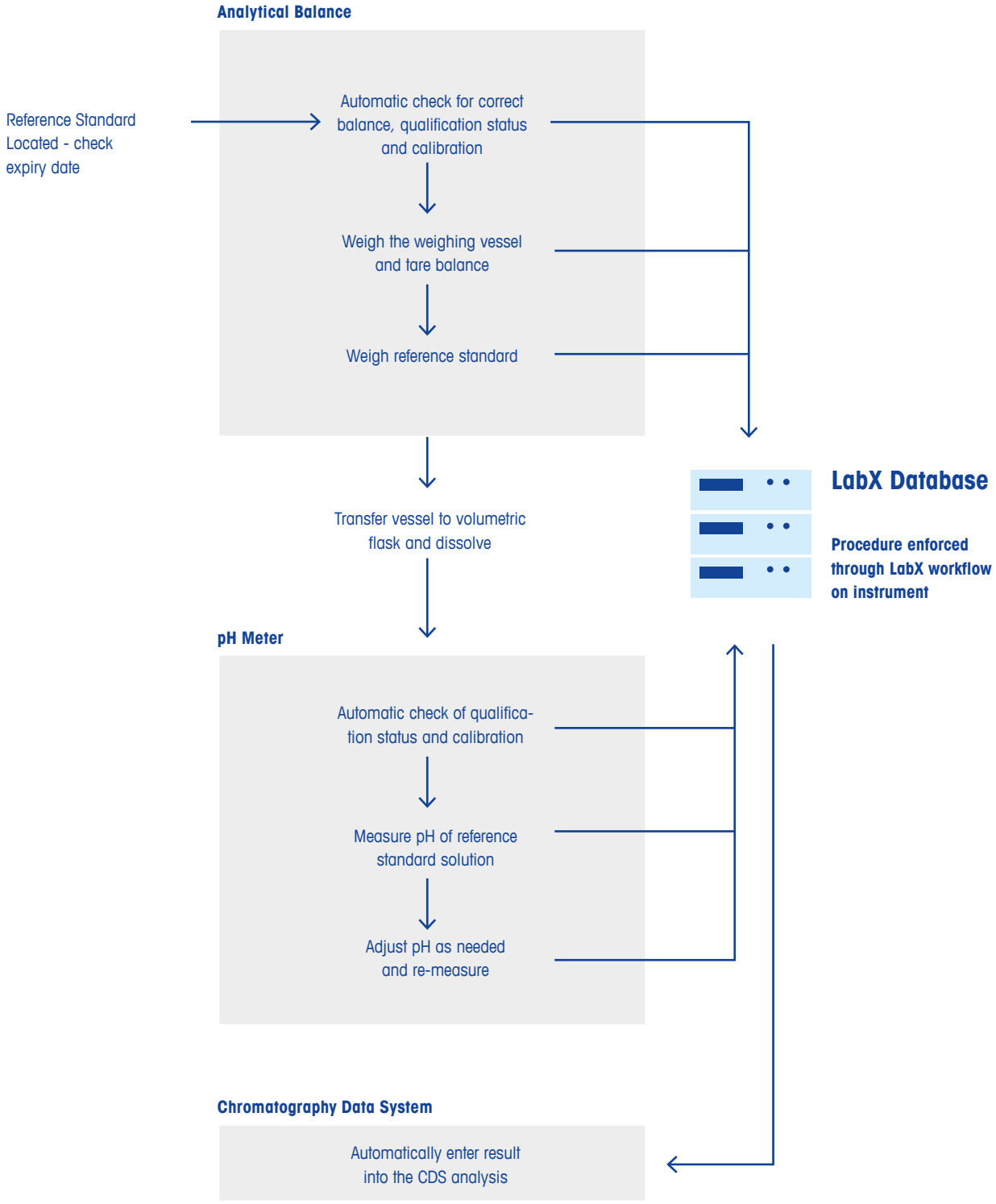

Figure 2: Electronic Workflow using LabX Software

3.2 LabX: An Integrated Electronic Workflow

The electronic workflow using LabX is shown in Figure 2.

As can be seen, the electronic workflow appears simpler and all data associated with the analysis is stored in the LabX database.

The workflow in figure 2 is far simpler and there are the following advantages for both the analyst performing the work and the second person reviewer:

- The qualification status of both instruments are contained in the LabX database, and if not qualified, the analyst cannot use the instrument
- Date and time of the work comes from the network time server, which itself is linked to a trusted time source; therefore the contemporaneous documentation of the work is assured
- The LabX workflow includes a check to require that the weighing is performed only on a balance with correct readability. This is also documented in the records of the work
- The mass set and acceptance criteria are in the LabX workflow for this procedure and the workflow will stop if the limits are exceeded
- Calculation of the analyte concentration is also automatically performed using a validated workflow
- The workflow automatically links the two instruments via the LabX workflow
- The pH measurements required are the calibration solution (with acceptance criteria) and the reference standard to ensure that the solution injected into the chromatograph is compatible with the mobile phase
- The reference standard concentration is transferred automatically to the CDS using a validated process.

The advantages to the laboratory are:

- Speed of analysis
- Speed of review
- ALCOA principles for data integrity are assured using the technical controls within the LabX application
- Total elimination of paper
- Assured contemporaneous recording of data
- Enforced workflow that mirrors the applicable SOPs
- Automated checks that the correct instrument is used in the process, each one is qualified and correctly calibrated
- Validated calculations are used throughout the process
- Automatic transfer of the reference standard concentration to the CDS

The second person reviewer profits from the advantages that:

- Many required checks that were tedious in the manual process are eliminated with LabX automation
- Issues that arise are easily highlighted when the LabX audit trail is reviewed or results are annotated for assessment – the data come to the reviewer not the reviewer to the data

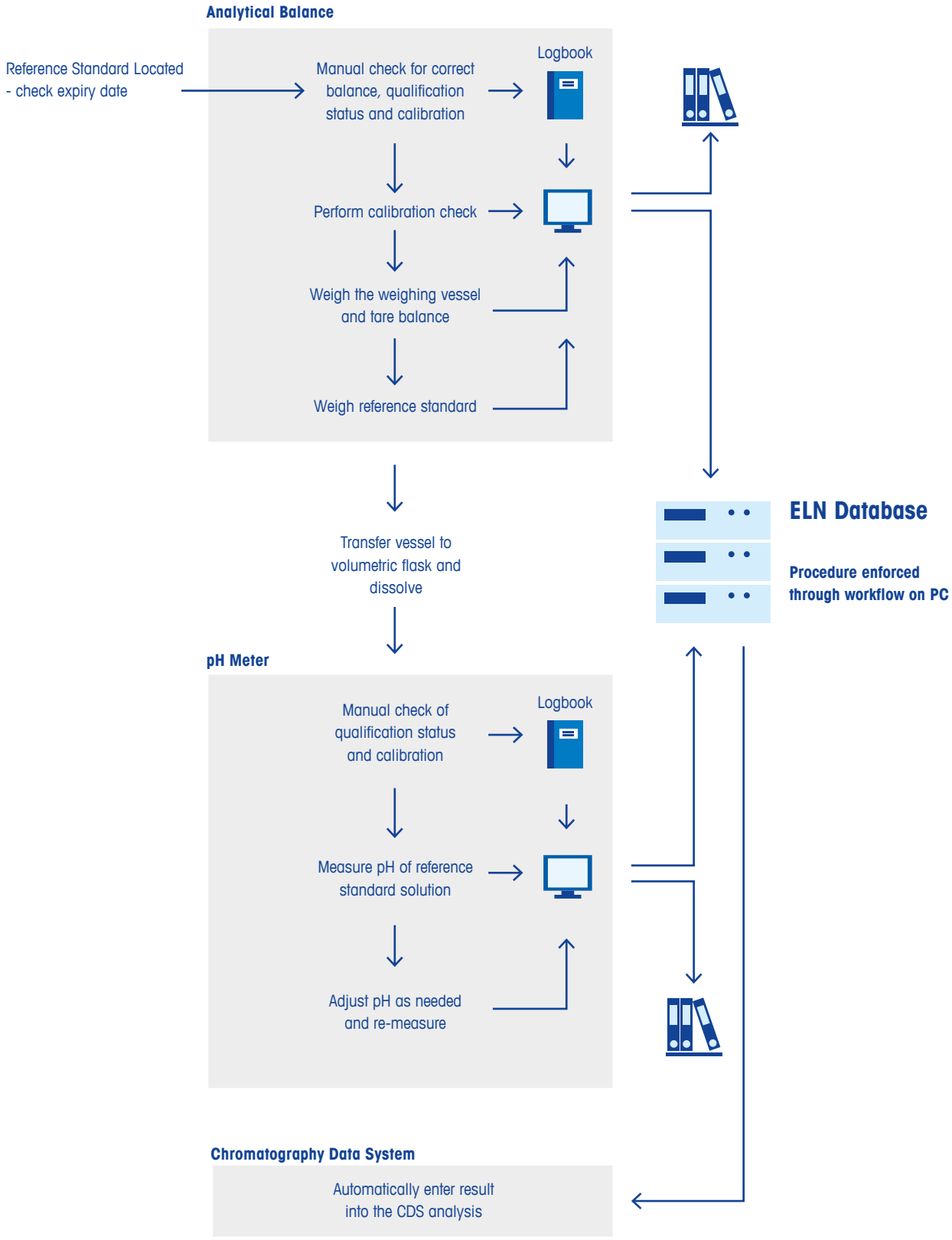

Figure 3: The Two Electronic Workflows in an ELN

3.3 ELN: Two Separate Electronic Workflows

If an Electronic Laboratory Notebook (ELN) is used the electronic workflows are shown in Figure 3.

When executing the ELN workflow the instruments are connected to the computerized system, but it differs from the electronic workflow with LabX in that:

- Instead of the instrument acting as a terminal, the principle means of setting up the analysis and communicating with the ELN requires a separate workstation in the laboratory.
- There are some practical complications for the use of this configuration as it requires the analyst to move between the analytical instrument and the PC terminal – beyond the obvious inefficiencies and depending on corporate IT settings, the PC terminal can timeout during the measurement.
- The ELN cannot determine if the correct analytical balance has been used
- The instrument screen only sends the result to the ELN database
- To connect the balance and pH measurement workflows bar code labels are used to identify the solution (not shown in the figure)
- The workflow between the balance and the pH meter is not linked in the ELN

The advantages of the ELN workflow are:

- The availability status of both instruments are contained in the ELN database and, if not qualified, the analyst cannot use the instrument
- The ELN will have its time and date stamp synchronized with the network time server. However, the analytical instruments have their own time and date stamps that have to be manually checked and changed especially following daylight saving changes.
- The mass set and acceptance criteria are in the ELN workflow for this procedure and the workflow will stop if the limits are exceeded
- Calculation of the analyte concentration is also automatically performed using a validated workflow
- The pH measurements required are the calibration solution (with acceptance criteria) and the reference standard to ensure that the solution injected into the chromatograph is compatible with the mobile phase
- The reference standard concentration is transferred automatically to the CDS using a validated process.

The advantages to the laboratory are:

- Speed of analysis
- Speed of review
- ALCOA principles supported
- Partial elimination of paper
- Two partially – enforced workflows that mirror the applicable SOPs
- Validated calculations are used throughout the process
- Automatic transfer of the reference standard concentration to the CDS

However, there are some disadvantages to the ELN workflow:

- Two terminals are now required – the analytical instrument and the workstation to communicate with the ELN. This can impact acceptance of the workflow by laboratory staff as they move between the two terminals
- Automated checks that the correct instrument is used in the process cannot be performed by the ELN and the reviewer must revert to a manual process to check this.
- Workflow (SOP) is still paper based as only partial task control is possible from the ELN
- Only part of the result data is captured by the ELN, therefore a hybrid solution is still in place where the lab must continue to maintain both paper and electronic data.

From the perspective of the second person reviewer there are still some advantages:

- Many checks that were required and were very tedious in the manual process are eliminated with automation. However, the ELN still requires two separate processes for the balance and the pH meter.

3.4 Automation and Compliance Comparisons Between the Three Processes

The three workflows so far discussed serve to exemplify manual and electronic processes, but it is evident that a well-founded/more thorough comparison of these processes is necessary to draw an objective conclusion.
To compare the manual and electronic processes look at table 1. This assesses the work involved in the two processes, clearly showing that the electronic process only has a single medium (electronic records) to handle the data generated in the process.

The validated electronic processes are transparent and far easier to review and inspect, and all records are in a central database.

- Automated process
- Transcription errors eliminated as all data acquired electronically
- Single data location
- Single medium to manage
- Option to print test report if required

Criterion	Manual Process		LabX Process		ELN Process	
	Effort	Risk	Effort	Risk	Effort	Risk
Controlled blank form issued and reconciled	High	High	N/A		N/A	
Number of manual transcriptions / manual entries to a computer	High	High	N/A		N/A	
Paper printouts to manage	High	High	Low	Low	Low	Low
Integrated electronic workflow enforced by technical controls	N/A		Low	Low	Medium	Medium
Communication with computer via a single screen	N/A		Low	Low	High	Medium
Check that the correct balance is used	N/A		Low	Low	High	Medium
Automatic transfer of standard concentration to the CDS	Manual	Manual	Low	Low	Low	Low
Potential for error or falsification	High	High	Low	Low	Low	Low
Speed of performing the process	High	High	Low	Low	Medium	Medium
Speed of reviewing the process	High	High	Low	Low	Low	Low

High Medium Low Not applicable

Table 1: Comparison of the Manual and Two Automated Processes

In comparison, the paper process has two printouts to manage plus a manual calculation and a manual entry of critical data to the CDS.

- Requires a controlled blank form to comply with current data integrity requirements
- Manual, paper based process
- Error prone
- Slow to execute
- Slow to review
- Two printouts to append to the controlled blank form
- Relatively simple to falsify (even when there is a controlled blank form)
- One manual calculation (this could be performed by spreadsheet with a hybrid system complicating the process flow with another printout and electronic file to manage)

Overall, the benefits for the laboratory are time saved in performing the work, allowing an increase in capacity, and the potential to release product earlier than with a manual process. Review can be automated, which allows for the possibility of reviewing audit trails by exception.

4. Driver 3: Return on Investment Pull

- Current situation: QC is at the end of the process and everybody waits until testing is complete before batch release. Caveat is that LabX only automates some assays, but these are the traditional wet chemistry analyses that can be rate limiting. Automation of other assays is required to achieve this.
- See the impact of this on company cash flow of earlier release to market
- If a batch is worth $1m and it takes 10 days to release what would be the benefit to the company if the release was reduced to 9 days?

5. Conclusions

This white paper has demonstrated the advantages of transition from a manual, paper based process to an automated process using an analytical balance and a pH meter (instruments common to every lab) as an example. With LabX the principles can be expanded to other analytical techniques such as Karl Fischer, titration, loss on drying, UV-Vis spectrophotometry, etc. The automation of the process and the time savings coupled with ensuring data integrity in a regulated GMP laboratory fully offset the purchase and validation costs of the system. Ultimately, combining LabX instrument control software to an ELN, LES or LIMS system brings the most benefit of workflow efficiency, data integrity support and total cost of ownership savings. And finally, after the short term pay back of the validated LabX system, and as the long term savings multiply in efficiency and batch release effort, an even the larger scale benefit is realized in the removal of the cost of 'non-compliance'.

6. Acknowledgement

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