White Paper

The Green Light for Weighing

Why Read This White Paper?

METTLER TOLEDO's new Excellence Plus range of analytical balances incorporates a green status light to confirm that all the factors required for precise and accurate weighing in a Good Manufacturing Practice (GMP) regulated laboratory are correct and that the balance is ready for use. If one of these factors is not ready, then the light turns yellow to warn but indicate that it is still safe to weigh, or red to tell an analyst not to proceed. When the problem is corrected, the analyst gets the green light for weighing.

Using these new balance features will help regulated laboratories to ensure that weighing operations are under control. Most importantly, it will help reduce weighing errors that could lead to out-of-specification, out-of-trend or out-of-expectation (OOS, OOT or OOE) results. Using these analytical balances helps to save time and effort by avoiding laboratory investigations caused by improper procedures.

Content

METTLER TOLEDO

Intended Audience

This white paper is addressed to analytical scientists and Quality Assurance professionals working in regulated laboratories in the Healthcare industry, or in companies supplying organizations within this industry segment.

Why is this White Paper Important?

Analytical balances are at the heart of virtually all quantitative analyses performed in regulated GxP laboratories. Accurate weighing is essential to the following critical steps within the laboratory:

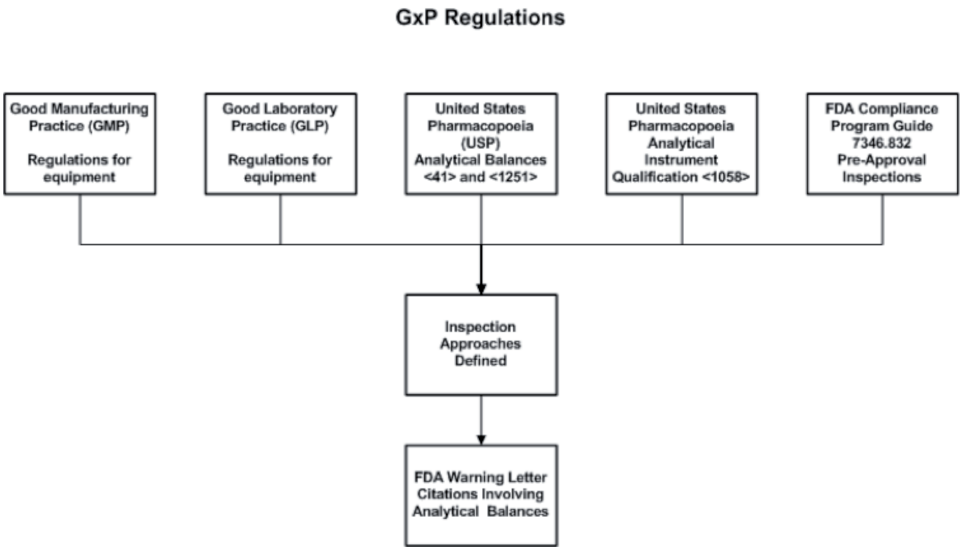
- Preparation of analytical reference standards;
- Taking aliquots of samples for analysis;
- Preparation of solution, buffers and HPLC mobile phases.

Therefore, analytical balances used in these laboratory operations need to be under control, as this is the essence of good analytical science. If there are problems with the analytical balance or the way it is used, then either of these two factors will have a major impact on the work of the entire laboratory.

Regulatory Perspective on Analytical Balances

In this section we will review the applicable sections of the GMP and GLP regulations, United States Pharmacopoeia (USP) general chapters for analytical balances, and the FDA's Compliance Program Guide 7346.832 for Pre-Approval Inspections (PAI). This is to determine the regulatory requirements for analytical balances and set the scene for defining approaches that could be taken in the event of an inspection. The overall scheme of this section is shown in Figure 1. Following that is a discussion of some FDA Warning Letter citations involving analytical balances when laboratories failed to observe the regulations.

Figure 1: Applicable GxP Regulations for Analytical Balances



GMP and GLP Regulations for Equipment: Under US GMP [Refs 1, 2] and US, OECD and Japanese GLP [Refs 3, 4 and 5] regulations, analytical balances may be described as either equipment or apparatus. In summary, these regulations simply state that equipment must be fit for its intended purpose, suitably located, adequately sized, and that any calculations performed must be checked for accuracy.

In contrast, EU GMP has two specific requirements for balances: they should have an appropriate range and precision, and they should be calibrated at defined intervals with records of this activity [Ref 6].

GMP Regulations for Laboratory Controls and Records: Under the laboratory controls section of the US GMP regulations [Ref 7, 8], QC laboratories are required to establish scientifically sound specifications and test procedures for the qualification and calibration of analytical balances. If a balance fails a test it must not be used until the problem is identified and resolved.

The laboratory records section [Ref 9, 10] requires complete data derived from all tests involved in release testing, including the weight of sample taken and any calculations performed on the data. In addition, complete records need to be maintained concerning the preparation of laboratory reference standards, reagents, and standard solutions used in testing, for example HPLC standards or mobile phase preparation. The EU GMP regulations for laboratory testing are simpler, but the requirements are essentially the same.

Both the EU GMP Chapter 4 [Ref 11] and US GMP regulations [Ref 12] require a balance use log for documenting in chronological order the use of the instrument, its calibration and maintenance, including dates and identity of personnel who carried out these operations.

United States Pharmacopoeia General Chapters for Analytical Balances: While the GXP regulations refer to manufacturing equipment in general, it is the United States Pharmacopoeia (USP) that states specific and detailed requirements for analytical balances. There are three applicable general chapters for analytical balances:

- <41> Balances;
- <1251> Weighing on an Analytical Balance;
- <1058> Analytical Instrument Qualification.

USP is in the process of replacing the existing general chapter <41> on Weights and Balances with two new general chapters. The revised version of <41> is now titled "Balances" and the new <1251>is called "Weighing on an Analytical Balance" [Refs 13, 14]. This is the new approach of USP; as general chapters are revised they will be issued in pairs with a mandatory test chapter (numbered less than <1000>) and a general information chapter (numbered between <1000> and <1999>) that provides good practice advice.

The revised USP <41> is the shortest chapter in the pharmacopoeia and requires that "accurate weighing" uses a calibrated balance that meets defined requirements for repeatability and accuracy. The repeatability test must be performed with a minimum of ten determinations of a test weight within the balance capacity. Minimum Sample Weight can be calculated from this achieved value for repeatability if a weight which is equal to or less than 5% of the balance capacity was used. The general chapter also requires that analytical balances are calibrated during installation and before operational use.

USP <1058> on Analytical Instrument Qualification (AIQ) [Ref 15] provides an overview of the process for the qualification of instruments and laboratory computerized systems. However, the details of the parameters that could be qualified are provided in the new draft USP <1251> [Ref 14]. USP <1251> includes sections on qualification (the overall process consists of design qualification (DQ), installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ)), balance checks, minimum weight, and good practices for weighing a variety of sample types [Ref 14].

Compliance Policy Guide 7346.832 (Pre-Approval Inspections): The increased incidence of falsification and fraud uncovered by the FDA since the Able Laboratories fraud case of 2005 [Ref 16] has resulted in new guidance for inspectors that became effective in 2012. The Compliance Program Guide (CPG) 7346.832 on Pre-Approval Inspections [Ref 17] has three objectives, the third of which is the Data Integrity Audit which focuses directly on the laboratory. This objective states:

> Audit the raw data, hardcopy or electronic, to authenticate the data submitted in the CMC section of the application. Verify that all relevant data (e.g., stability, biobatch data) were submitted in the CMC section such that CDER product reviewers can rely on the submitted data as complete and accurate.

This objective is achieved by inspecting the laboratory records, as well as looking at both paper and electronic records and ensuring that they follow a logical path from their creation through manipulation to reporting. The CPG goes into more detail as follows:

> During the inspection, compare raw data, hardcopy or electronic, such as chromatograms, spectrograms, laboratory analyst notebooks, and additional information from the laboratory with summary data filed in the CMC section. **Raw data files should support a conclusion that the data/information in the application is complete and enables an objective analysis by reflecting the full range of data/information about the component or finished product known to the establishment.** Examples of a lack of contextual integrity include the failure by the applicant to scientifically justify non-submission of relevant data, such as aberrant test results or absences in a submitted chromatographic sequence, suggesting that the application does not fully or accurately represent the components, process, and finished product.

Therefore the regulatory requirement is for a laboratory to demonstrate that they have the complete records of any analysis used to support not only a pre-approval inspection but also any product analysis.

An Inspector Calls

One certainty of working in a GxP laboratory is that there will be regulatory inspections. The reasons for inspections can be regular and scheduled facility visits, study-specific or pre-approval visits, or unannounced for-cause inspections. Inspections may be from a single regulatory agency or multiple agencies, depending on where the company operates and where its products are sold. In addition, there will be internal audits carried out by local or corporate personnel or by third parties if the laboratory is a Contract Research Organization (CRO) or part of a Contract Manufacturing Organization (CMO).

However, with the introduction by the FDA in 2009 of the post 483 observation program [Ref 18], readiness for inspection is essential. This program requires the laboratory to have a complete response to all 483 observations or non-compliance within 15 working days after the inspection.

Inspection Approaches Defined

From the regulations presented above, we can derive the following ways that an inspector will review an analytical balance:

- The analytical balance must be specified, installed and qualified correctly against the specification, with appropriate qualification documentation.
- The balance must be calibrated at installation and at defined intervals thereafter to ensure that it remains accurate and within operating tolerances. Records must exist of these calibrations.
- Specifications and operations involving analytical balances must be scientifically sound.
- Analytical balances failing calibration tests must not be used until the problem is resolved.
- Any maintenance or service carried out is recorded and documented.
- A use log is maintained by the laboratory that shows, in chronological order, when the balance was used and what was weighed.

Handling Inspections

As the owner of an analytical balance, what can you expect when an inspector comes to your laboratory? Typically, the inspectors will start with your organization's pharmaceutical quality system and look at document control, training records, policies and procedures, and deviation management. Having completed inspection of the quality system, the next focus is the laboratory. An inspector will check your laboratory against the GMP regulations and pharmacopoeial requirements. The key areas are shown in the section above, which can be used as a checklist for inspections.

As an analytical balance is at the heart of quantitative analysis in all regulated laboratories the scope of inspection can be very wide. However, the inspector may start by wanting to know if the balance is under control, and if it is qualified, calibrated and maintained as follows:

- How was the analytical balance installed? This is typically done by reviewing the instrument's DQ, IQ and OQ documents.
- How was the analytical balance calibrated while in use? This will be checked by looking at the records of external calibrations using reference weights, routine testing records, and the internal adjustments of the balance.
- How is the analytical balance serviced and maintained? Here the service records will be inspected to ensure that adequate control is exercised.

Typically an inspector will start with either the analytical portion of the batch records or by selecting an item from the balance log book and beginning the inspection from there, tracing how the weight of a reference standard has been prepared, labeled, stored and used. This will include the preparation of a solution with the identity, storage conditions and expiry date noted when it was prepared. That may be expanded to include the use of the

solution in the analysis of various batches of product or in a study, and could include disposal if the solution had expired. Another approach is to determine how a sample has been analyzed and if the weight of the aliquot was used in calculating the reportable result.

Warning Letter Citations

Regrettably, some FDA inspectors have found that certain laboratories are falling short in their approaches to compliance of analytical balances, as we can see in the following excerpts from warning letters.

Warning Letter Citation 1: The lack of calibration records and instrument use logs is a major deficiency that casts an overall shadow over the work of a laboratory, as we can see from the first citation example:

> In your response, you state that you will **author calibration programs for instruments and autoclaves and implement use logs for your balances** and pH meters. Your response is inadequate as you have not included a review of the calibration status of all equipment and instrumentation used in the production or testing of API intended for the U.S. market.
> (FDA Warning Letter March 2012)

As we are working in a "systems" environment, a problem with one instrument has consequences throughout the laboratory.

Warning Letter Citation 2: Even if a laboratory calibrates its balances using external weights, there is no point in just writing down the results of each weighing. The values need to be compared with specifications to check that the balance is working within pre-defined tolerances.

> Our investigator reviewed your previous **annual calibration records for <redacted> for balances … and found them to be outside of specified tolerances.**
> (FDA Warning Letter September 2011)

If the results lie outside of the set tolerance, then the analytical balance must not be used. Furthermore, the deviation must be documented, investigated and rectified; as part of the investigation you need to know how many product batches were analyzed while the balance was out of tolerance, and the impact this would have on the release of each one.

Warning Letter Citation 3: Even if you perform calibration checks, are they the right calibration checks? Remember that an analytical balance has an operating range which needs checking to ensure that the balance is working correctly. This needs to be done at both ends of the operating range so that the balance is assumed to work across the whole range, rather than with a single weight – as in this citation:

> Failure to calibrate, in accordance with written procedures and an established schedule, weighing equipment critical for ensuring the quality of APIs. For example, **your firm failed to properly calibrate the scale within the range of its intended use. Although the scale was calibrated to 500mg (0.5g) and underwent daily verifications to 100mg (0.1g), the scale was used numerous times to determine laboratory sample weights as small as 10mg (0.01g).**
> (FDA Warning Letter April 2011)

The message here is clear: interpolation within a range is acceptable, but extrapolation from a single value is not. Therefore the operating range needs to be defined in the Design Qualification [Ref 15] and be linked through the OQ to the operating use of the analytical balance.

Warning Letter Citation 4: In addition, USP <41> requires a minimum weight determination for analytical balances to ensure that they are not being used outside of their operating range. This is the argument of readability (the balance shows four places of decimals) versus accuracy (but how close to 10mg is the actual result?).

> Failure to have an adequate performance qualification (calibration) program for QC laboratory instruments. **You fail to challenge the analytical balances for minimum weight, measurement for uncertainty, and drift value.**
> (FDA Warning Letter October 2010)

Summary: Being in compliance is always easier and cheaper than being out of compliance and having to correct mistakes. It is also sound science [Ref 7, 15] and good weighing practice [Ref 19].

Returning to the laboratory inspection and the Compliance Policy Guide 7346.832 [Ref 17]:

> During the inspection, compare raw data, hardcopy or electronic, such as chromatograms, spectrograms, laboratory analyst notebooks, and additional information from the laboratory with summary data filed in the CMC section. **Raw data files should support a conclusion that the data/information in the application is complete and enables an objective analysis by reflecting the full range of data/information about the component or finished product known to the establishment.** Examples of a lack of contextual integrity include the failure by the applicant to scientifically justify non-submission of relevant data, such as aberrant test results or absences in a submitted chromatographic sequence, suggesting that the application does not fully or accurately represent the components, process, and finished product.

The key point to demonstrate to any inspector during an inspection is that you are in control. This is achieved by demonstrating that you are in compliance with the regulations and your own procedures and that your laboratory records are complete and you can demonstrate the integrity of the data.

Regulatory Perspective on Analytical Balances

How can METTLER TOLEDO's new analytical balances help your quest for quality and regulatory compliance?

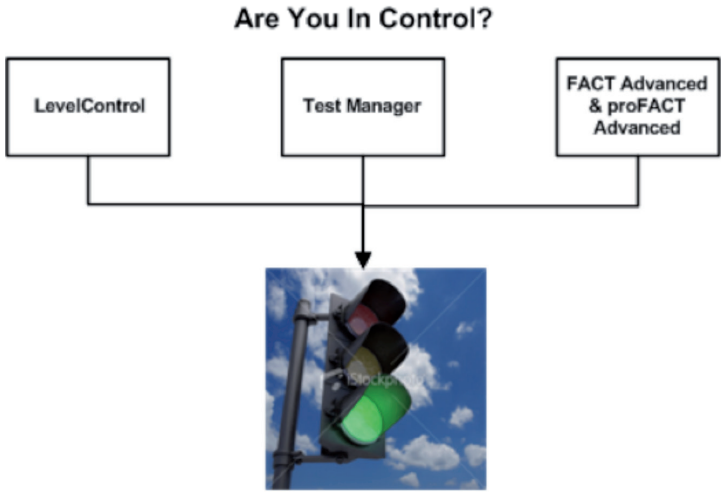
Introducing the Status Light

The answer is very simple. A status light is built into the base of the new range of Excellence Analytical Balances XPE / XSE. This indicates whether the factors for good weighing practice are within acceptable ranges and, if not, warns the user that the balance is not ready for use. The status light works on the principle of a traffic signal:

- Red means an error. The balance must not be used until the error is corrected.
- Yellow indicates a warning, for example that the Test Manager has pushed a test to the balance or you are operating in the grace period before a recalibration is required. The balance can still be used.
- Green for go. No problems detected and the balance is ready to weigh.

The safety features linked to the status light are designed to ensure the accuracy and correctness of the balance measurement. These features are shown in Figure 2 and we will discuss each one in more detail below.

Figure 2: Balance Factors Linked to the Status Light



LevelControl

A level balance is an essential requirement for accurate weighing, especially for small amounts of sample or reference standard. Typically an analytical balance has a spirit level at the back of the unit where it may be difficult to see, especially if the balance is located in a fume cupboard or if the space around it is restricted. Many laboratories require that the balance and the surrounding area are routinely cleaned to remove any potential for contamination. If the balance is replaced wrongly and it is not level, there is a feature to detect this called LevelControl.

This will automatically and continuously detect if the balance is not level and warn the user with a red signal. When the LevelControl detects that the balance is not leveled, a warning will appear on the screen with a status icon in the upper right hand of the display, and a warning beep will sound. Then, on the terminal screen, a graphical representation appears of the spirit level with the bubble in red. As the balance is leveled in real time, the bubble turns successively yellow and then green when the level is correct. The status light at the front of the balance also follows the same sequence. The warning and correction of the level is recorded within the balance and can be printed out if required by the user, if LevelControl is being used in combination with the Test Manager. If the balance is connected to a LIMS or ELN, then the leveling information can be passed to the database of either application in combination with the external LabX Balances SW.

Of course, the physical spirit level is always available to check that the software works, or it can be used if the software fails.

Incorrectly Placed Balance Pan

As a further measure to ensure correct weighing, there are sensors to detect whether the balance pan is out of position. This is particularly important if the balance pan has been cleaned, or a different type of balance pan is used. In either situation the balance can check to see if a pan has been placed incorrectly in the instrument. In this case the status light turns red and a warning message appears on the balance screen. Once the balance pan has been correctly positioned the warning message disappears and the status light turns green.

Internal Adjustment: proFACT and proFACT Advanced

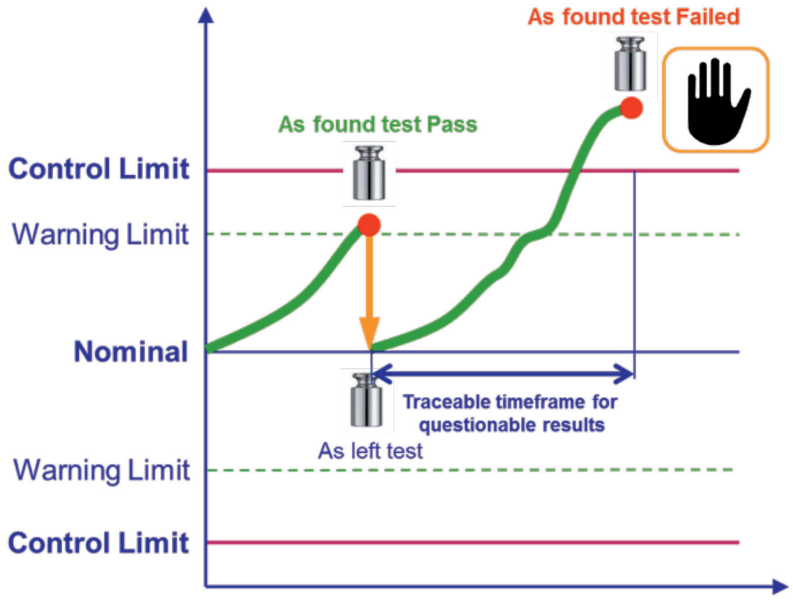
FACT is an acronym for Fully Automated Calibration Technology. The largest source of error in an analytical balance occurs due to fluctuations in the environmental temperature. FACT is a mechanism whereby the analytical balance has a set of internal weights that are calibrated at the factory to eliminate measurement drift caused by temperature fluctuations.

Internal Adjustment of an Analytical Balance: A balance can be adjusted using the internal weights, with a user-definable frequency of the check and adjustment. Inside the analytical balance is a temperature sensor that can be set by a user to trigger an internal adjustment. Thus, when the environmental temperature rises or falls by a user-defined amount, e.g. between 1-3°K, the balance can begin an automatic internal adjustment to ensure its continued accuracy. When this occurs, the status light flashes green and the balance is blocked during this internal adjustment. The status light shows steady green when the process is complete.
There are two types of adjustment possible:

- proFACT is a user-defined time and temperature triggered internal adjustment, for the highest process safety.
- proFACT Advanced functionality provides a measure of change from the last FACT adjustment to the adjustment about to be performed. (This provides the "as found" and "as left" calibration measurements of an analytical balance.)

This information provides the before and after measurements of the balance and shows how much the instrument has been adjusted. In addition, the user can set warning and action limits and if the test was passed or failed. This information can be printed out for the analyst to sign and place in the balance log book.

Figure 3: Warning and Control Limits of External Balance Calibration



Using these features enables the user to schedule a check of the balance sensitivity and non-linearity either when the environmental temperature changes by a pre-defined value, or on expiry of a pre-defined time period, see Figure 3. This means that the balance can be adjusted automatically to ensure that it remains within specified limits. Using the new proFACT Advanced feature can avoid or reduce OOS or OOT results.

The new USP Chapter <1251> [Ref 14] describes a risk based approach to balance testing, explaining that balances with internal adjustment weights may be tested less often by external weights, depending on the level of weighing risk. However, laboratories must decide individually on the frequency of external calibration and how much reliance to place on internal calibration.

The internal adjustment is accomplished using two weights that check the top and bottom of the balance's range. As you will remember in Warning Letter Citation 3 earlier, a laboratory was cited for not calibrating an analytical balance throughout the operating range of the instrument. With the Excellence Plus range of analytical balances, FDA expectations are met with the internal adjustment over the operating range of the balance. Interpolation is used, not extrapolation.

Using Internal Adjustment in Conjunction with External Calibration: Although proFACT and proFACT Advanced functions can be disabled by a user, this will be unlikely in a regulated laboratory as it helps to reduce the amount of external calibration required. It is very important that regulated laboratories do not rely solely on the internal adjustment features of an analytical balance. Internal adjustment needs to be used in conjunction with a program of external calibration using mass sets that are traceable to national or international standards. The FDA's website contains advice regarding internal adjustment and calibration [Ref 20]. The advice takes the form of a question and answer:

> **Question:** Many leading analytical balance manufacturers provide built-in "auto calibration" features in their balances. Are such auto-calibration procedures acceptable instead of external performance checks? If not, then what should the schedule for calibration be?
>
> **Answer:** The auto-calibration feature of a balance may not be relied upon to the exclusion of an external performance check (§211.68). For a scale with a built-in auto-calibrator, we recommend that external performance checks be performed on a periodic basis, but less frequently as compared to a scale without this feature. The frequency of performance checks depends on the frequency of use of the scale and the criticality and tolerance of the process or analytical step.

In essence, you cannot rely solely on the internal checks performed by the balance; a laboratory has to perform checks on the balance performance using externally calibrated weights. However, the FDA guidance continues with some words of caution:

> Note that all batches of a product manufactured between two successive verifications would be affected should the check of the auto-calibrator reveal a problem.

What this means is, if you perform an annual check using calibrated masses and there is a problem, then this will cast a shadow over all work performed since the previous check that was within pre-defined limits, as shown in Figure 3. However enabling proFACT advanced will help you manage some of the major factors that influence accurate weighing in a regulated laboratory and reduce the weighing sources of OOS results.

Given the criticality of weighing in a regulated laboratory, management might want to carry out a risk assessment and decide whether or not to reduce the time period between external calibration checks. However, using a risk based approach to external calibration with internal adjustments via proFACT and proFACT Advanced will provide confidence in your weighing results and that your balance is under control.

TestManager™

One further way to ensure accuracy and compliance of balance checks is to use the TestManager function of the Excellence analytical balances XPE and XSE. Regulated laboratories will use external mass sets to check that the balance is still within pre-defined limits, and this will be under the control of a Standard Operating Procedure (SOP).

TestManager allows an authorized user to register the masses to be used for external checks within the balance memory with information such as: number, class (e.g. E2, F1), nominal and calibrated masses, tolerance, weight set number, and the due date for their recalibration.

Next, the steps in the SOP can be defined in the balance so that the instructions appear on the screen in the correct sequence to lead the analyst through the test and so ensure compliance with the SOP. The time for conducting repeatability and sensitivity tests can be programmed into the balance to ensure that they occur at the pre-defined intervals. These procedures are protected by administrator rights so that only authorized individuals can change them. They enforce SOP compliance by ensuring that the actual process matches the documented process.

When a calibration is due, the TestManager turns the status light to yellow to warn a user that the calibration is imminent. The balance can still be used for normal operations. However, if the calibration becomes overdue, then the status light turns red and the balance could be blocked, thus enforcing an external calibration.

When the procedure is conducted, TestManager can detect if the wrong mass is being used for the test and so correct some basic mistakes. On completion of the procedure, a printout is produced via the attached printer for the analyst to sign and place in a laboratory notebook or an analytical batch record. If the test passed, then the status light turns green again and the balance is released for operational use. However, if the test failed the balance remains blocked and hence ensures compliance with 211.160(b)(4) [Ref 8], which can trigger a service request.

Conclusion

Getting analytical balance weighings right first time, avoiding laboratory investigations, and showing inspectors from regulatory agencies that you are in control of the process are major challenges in today's regulated laboratories. To help laboratories meet these challenges, METTLER TOLEDO has designed the Excellence Plus range of analytical balances with the following features:

- The status light on the front of the control panel gives any user the green light for weighing by showing that major functions of the instrument are under control and within acceptable limits. A red light indicates there is something to be resolved before weighing can safely go ahead.
- Control of the internal calibration features of the balance is now user-defined. The temperature trigger for an internal calibration can be set between 1-3°K. In addition, the "as found" and "as left" results of an internal calibration are recorded for review.
- TestManager defines the masses to be used for external calibration, the acceptance limits of the results, and the time interval until the next calibration.

These features combine to ensure the accuracy and correctness of analytical balance measurements for regulated laboratories and provide confidence when facing an inspector.

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