Have You Checked Your Device?

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When a regulation calls for device checks — what does this really mean?

One of the less discussed areas of the *Electronic Records, Electronic Signatures final rule* (1) is the section on device checks for systems. This little gem is hidden in §11.10(h) and states:

"Use of device (e.g., terminal) checks to determine, as appropriate, the validity of the source of data input or operational instruction."

OK, so what does this mean for the laboratory chromatographer? How can we comply with this part of the regulation? We'll look at some examples of device checks that can be used to confirm the validity of source data entered into the computer systems used in your chromatography laboratory. You could also be surprised to find out that you may already use device checks without realizing it.

From any perspective, look at a device check as a second operator reviewing your work as you enter it into a computer system. This is not Big Brother looking over your shoulder but a means of preventing wrong data being entered and thus avoiding bigger problems developing later on when it will be far more difficult to back out with grace.

We'll start by looking at the simplest device checks first and work our way onwards to more complex examples later. The device checks that you could have will be covered in the following areas:

- manual data entry
- automated data entry using barcodes
- analytical balance connected to a laboratory information management system (LIMS)
- equipment connected to a chromatography data system (CDS).

I'm not claiming that this list is exhaustive but these are used as examples of what constitute device checks.

Manual Data Entry

Manual data entry using field formatting is one of the simplest device checks that you could use. Here the data entry field can be formatted for the type of data to be entered. For example, the field can be formatted to accept either

- numeric data
- alpha data
- alphanumeric data.

One typical example that may be recognized by many readers is the use of the formatting field function within a spreadsheet, such as Excel. A developer of a spreadsheet macro or template can select the type of data to be entered into a cell, row or column using the formatting options available within the application itself. For example, the developer can format the cells so that only numbers can be entered (Figure 1). Furthermore, the number of figures or decimal places can be formatted into the selected fields. Therefore, you can see that device checks can be implemented relatively simply, even in a spreadsheet.

Device checks can be taken further with error-trapping routines — when data in the wrong format are entered into the field, a message can be sent to the user requesting the re-entry of data. This saves committing data to a field and then having to modify the data later, with an associated entry in the audit trail explaining the change.

However, there are limitations to this approach as the check can only verify that data entered are in the specified format, but not that data are correct or within any expected limits. However, increasing protection (more device checks) can include cell protection whereby calculation formulae and unused cells can be locked, thus preventing unintentional use or alteration.

There are limitations within the formatting of a spreadsheet unless visual basic programming is undertaken, but LIMS data entry can take this concept further. Imagine you have a field for pH value. The options for data input range from 0–14; however, because of the nature of the sample and the analysis, the results will fall in the range from pH 4.0 to 7.0. Therefore, a device check can be set up to ensure that only numeric data in the range of 4.0 to 7.0 can be entered into the computer, otherwise an error message is generated to alert the user that a wrong value has been entered. The field verification can be set to ensure that only positive data within the range and number of significant figures can be entered.

Validation of this field is relatively simple: when data within the limits are entered they should be accepted without error, as should values entered at the limits of the specification, pH 4.0 and pH 7.0 (boundary testing). However, when values of 3.9 or 7.1 (out of limits or stress testing) are entered, both should be rejected with an error message. If the field has been set up to take

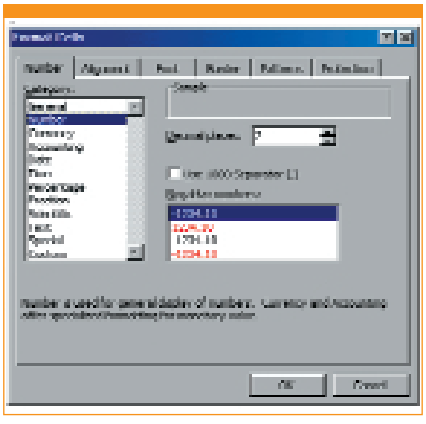

Figure 1: *Formatting cells in a spreadsheet program.*

only positive numeric data, then negative values entered into the field should be rejected, as should alpha characters.

Moreover, the device check can also reject correct but mistyped values. Take, for instance, the value 4,5 — it looks correct but notice the comma instead of a full stop; the device check should ensure that this value is rejected and the user invited to re-enter the value correctly. Although the original but wrongly delimited result may be accepted by a system, there can be problems further down the processing path if the value is used in a further calculation. In this instance the mathematical calculations may malfunction later as the number is not in the right format, because of the comma, causing a bigger problem than preventing the entry in the first place.

Drop-Down Menus

A further refinement of implementing a device check using manual data entry is to use a drop-down menu or to browse a field of options and select the one most appropriate. This is where you want to avoid typing or require consistent data input.

A typical example for this can be the reason for change input into an audit trail when modifying data (Figure 2). When reviewing analytical results it would be good to see consistent annotation such as "Below limit of quantification," rather than a ragbag selection of the following:

- <LOQ
- CMI or *can't measure it*
- peak is below the lowest standard in calibration curve.

And I've not even mentioned the misspelled entries. If you are looking to annotate data modifications, the last thing you want Quality Assurance or the Inspectorate to see is a series of inconsistent, incoherent or misspelled words. After all, consider your laboratory's image; on second thoughts, perhaps I'll not continue.

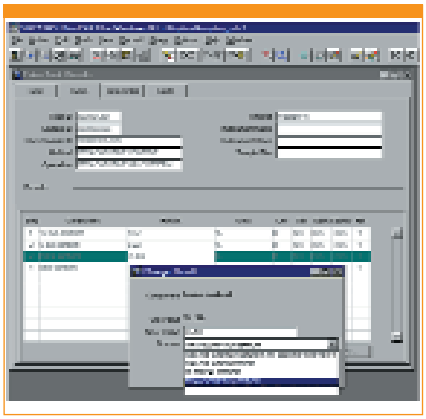

Figure 2: *Entry of a 'Reason for Change' into an audit trail from a drop-down menu.*

"Device checks can be implemented relatively simply, even in a spreadsheet."

During the system configuration of a LIMS or a CDS, a system manager can enter a list of reasons for change into the audit trail that are typically used by the laboratory now in their manual processes and Standard Operating Procedures. These can be verified and checked so that they can be used before the system goes live. Operational use is very simple: when a need to enter an audit trail entry occurs, then the drop-down menu appears, inviting a user to enter the reason for change by selecting a field from the options already entered. Simple and easy, provided the user is trained and has at least three neurones working in the correct sequence.

Device Checks for Equipment

We have just looked at some simple device checks with data entry into a spreadsheet or computer system audit trail. Of course within our laboratories we have more complex equipment and computer systems, so how can we use device checks here? We'll look at three examples:

- barcode data entry
- balance data capture using a LIMS
- chromatography equipment linked to a CDS.

We'll see that procedures you use normally in your day-to-day work can be device checks when used within a data system or equipment is connected on-line.

Barcode Data Entry

Barcodes are very versatile and can be used not only for identifying samples in a LIMS using sample numbers, but also for instructions for a computer system to execute. For example, test identities can be printed onto paper as barcodes and this paper can be scanned to select the individual tests allocated to a sample. Worksheets can also be barcoded and scanned to confirm that the correct worksheet is being used for a particular analysis. All the users need to do is point the laser reader at the correct barcode and everything is OK — just train them to aim straight!

Balance Data Capture by a LIMS

Further examples of device checks can be found when you connect a balance to a LIMS (Figure 3) where the user can send the balance reading to the computer system. Here, the balance is connected to the LIMS and when appropriate the weight can be transmitted from the balance to the LIMS by the operator.

Device checks can be developed in several ways. The most obvious is a routine calibration and maintenance programme. As everyone realizes the criticality of an analytical balance, this is undertaken in all laboratories I have visited without exception; furthermore, we all check that the balance works with a regular check against calibrated weights. The records of this are usually written down into a laboratory notebook (paper records!).

In normal use, an electronic balance will not fall under the remit of 21 CFR Part 11. As there is no durable medium to write a record to, all data are held in volatile memory. However, if a balance is connected to a LIMS as shown in Figure 3, can we use our existing practices to meet the requirements for device checks? Of course we can.

Let me describe one that was implemented on the first LIMS I was involved with in 1985, just to show you that device checks are not just a requirement of 21 CFR Part 11 but plain, analytical common sense, especially as weighing is the start of many analytical

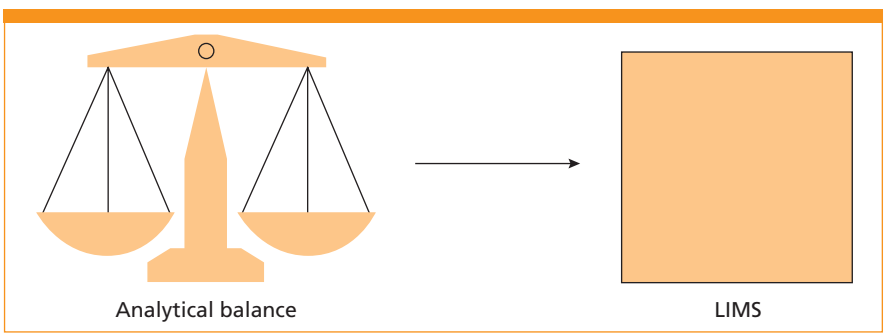

Figure 3: *Interfacing an analytical balance with a LIMS.*

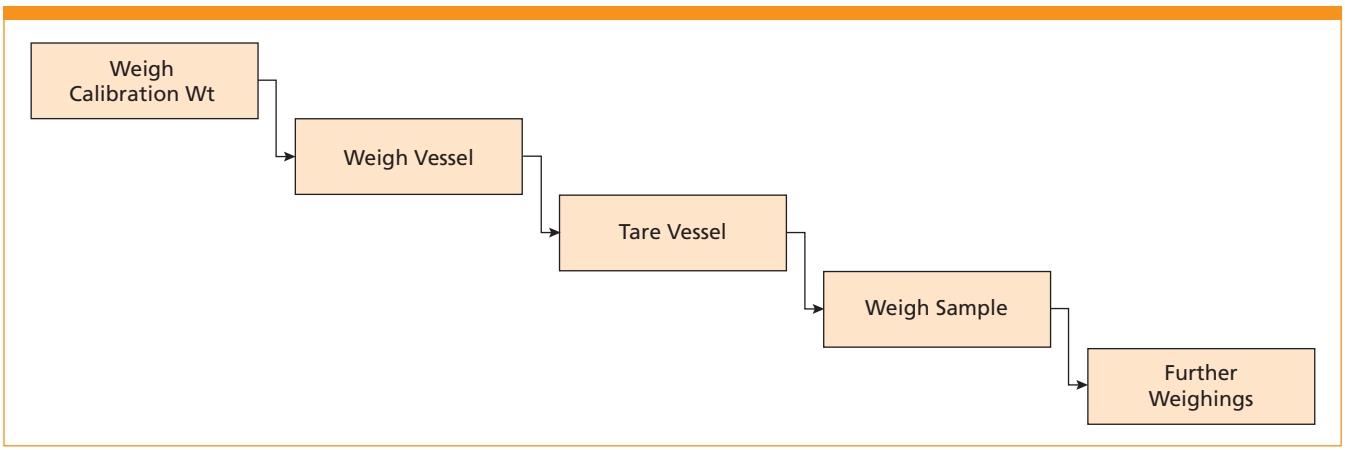

Figure 4: *Process of weighing a sample for 21 CFR Part 11 records.*

procedures. Getting the weight wrong can impact so many parts of an analytical run.

At the start of the session, the user ID would be captured from the user identity at log-on. The balance would be checked by weighing a calibration weight to see whether it was within specification against a predefined limit within the LIMS. Here is a device check over 10 years earlier than required by the 21 CFR Part 11 regulations. The LIMS held all calibration weighings that could be extracted and analysed over time to see whether there was any change on balance operation. Thus, you can eliminate the laboratory notebook currently used for recording the weighings manually whilst, in my view, increasing your compliance with little or no change in working practices.

Fast forward to today and let's look at how we can modify the process to fit better into the requirements of 21 CFR Part 11. The process flow is described in Figure 4. The device check is first to weigh a calibrated weight and see whether the result is within the required specification (same as described above). Next a vessel will be placed on the pan or scale and weighed; this value is usually tared and then the analytical reference material or sample is weighed. The results that could be transferred to the LIMS are

- calibration weight (with confirmation that the reading is within specification)
- vessel weight
- tare reading
- sample weight (further manipulations are possible such as salt weight to base weight conversions or purity calculations)
- further weights (loss on drying experiments with calculation of percentage water).

These values will provide you with the device checks and the audit trail that your weighing was accurate and performed in the correct sequence, as all readings will be time and date stamped. This makes the device check a very valuable design feature for a laboratory or any other computer system.

Chromatography Equipment Linked to a CDS

The types of device checks that can be used in most chromatography laboratories fall into three basic types:

- qualification of the chromatograph
- calibration of the analogue-to-digital (A/D) converter used to acquire data from the detector output
- system suitability test used to confirm that the analytical run is acceptable.

We'll look at each in turn and see what the impact of each can be on the quality of results generated.

Qualification of the chromatograph: The chromatograph should be regularly maintained and qualified to ensure that it performs as intended. Parameters to be qualified are those that are critical to consistent operation of the chromatograph; for example, the following parameters should be qualified for an automated gradient high performance liquid chromatography (HPLC) system with an ultraviolet (UV) detector:

- pump flow-rates and gradient formation
- precision, linearity and accuracy of autosampler injection
- column heater temperature accuracy and precision
- detector wavelength accuracy and photometric linearity.

The classic paper is by Furman et al. (2), with other information in an earlier "Questions of Quality" column (3) and in a paper by Burgess et al. (4) recommended for further reading on the subject.

Qualification of the equipment is important: if you state a detector wavelength of 241 nm, you know that it is correct if it has been checked against a traceable holmium standard. However, the failing of holmium is that it cannot be used to qualify wavelength in HPLC detectors below 241 nm, so there will be a problem with your device check if you measure compounds below this. Alternative standards should be used as well. If your detector is not set at the correct wavelength, this can affect your method's sensitivity and limits of detection: important if quantifying traces, for example, bioanalysis and impurities.

Qualification of your chromatographic equipment is also very important if you are involved in technology transfer, even with the laboratory next door. If you set a flow-rate of 1 mL/min on your pump, do you really only get 0.8 mL/min delivered? If you don't check, you don't know. Transferring the method means that you may waste time and effort trying to reproduce an irreproducible one because of a failure to qualify a chromatograph.

Calibration of the A/D units: Is the A/D unit that you are using calibrated and reproducible? In an earlier "Questions of Quality" column (5), we looked at data for A/D unit calibration. For most A/D units, the performance was consistent over a number of years. This is important to know, but don't assume your A/D units will operate the same — if you don't check, you won't know.

The usual way to check is to use an external calibrated signal generator. One of the main failings of these is that they do not generate an out of specification signal; you'll have a series of Gaussian peaks that you can select from a menu, and they will increase in size either arithmetically or geometrically. For instance, if you have an A/D chip with an input between 0 and 1 V,

the signal generator will generate output voltages in this range only; there is no boundary testing at say 997, 998, 999 and 1000 mV, and no stress testing at 1001 and 1002 mV. Are we paying lip-service to calibration or are we going to design tests correctly?

You could outsource A/D unit calibration to an external company. This could be the CDS vendor or a laboratory certified to ISO 17025, but regardless of the approach you must have a certificate of calibration that includes traceability of measurement to national or international standards. Don't get fobbed off with vague statements about being conducted to equivalent standards; you are not getting full traceability. Also make sure, if you do outsource, that the measurements and calculations are scientifically correct. I have reviewed external calibration of A/D units for which three calibration measurements have been made at each point over the range, and a mean and standard deviation calculated. This is statistical rubbish; ensure you have six measurements to generate meaningful data.

System suitability tests: "What," I hear you say, "can a system suitability test (SST) be a device check?" Yes. Consider the situation; you have a chromatograph that you have set up for the analysis of your favourite compound. As required by the *United States Pharmacopeia* (6), an SST needs to be performed and the SST samples are distributed throughout the run to demonstrate consistent performance of the analysis.

Remember the requirements of the 21 CFR Part 11 regulation dealing with device checks: "Use of device (e.g., terminal) checks to determine, as appropriate, the validity of the source of data input or operational instruction." How do you determine whether the chromatography run is acceptable? The answer is if the results from the SST samples meet the criteria defined in the SST for the method. Therefore, the validity of the source data (chromatographic results) is determined by the device check (SST results within acceptable limits). *Quod erat demonstrandum!*

Use of a CDS can automate the SST calculations and can determine whether the results are within preset limits. You can go further and set up warning and action limits as shown in Figure 5.

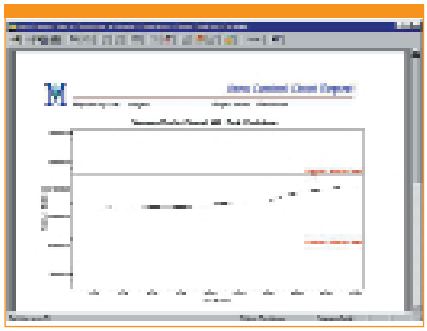

Figure 5: *System suitability test parameters calculated by a chromatography data system.*

Summary

Device checks are basic common sense that are intended to help us get the right input into a computerized system. These checks are many and varied, and I've just covered a few to give you an idea of what they are and how helpful they can be.

References

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(4) C. Burgess, D.G. Jones and R.D. McDowall, *Analyst,* **123**(9), 1879–1886 (1998).
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(6) <621> Chromatography, United States Pharmacopeia XXIV 2000, United States Pharmacopeia Commission, Rockville, Maryland, USA.

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