QUALITY MATTERS

The proper use of certified reference materials for analytical instrumentation qualification

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The proper validation of an analytical instrument is a topic that has long concerned me. Laboratories accredited to ISO/IEC 17025 put much effort into validating a method, but the starting point should be that the analytical system is working properly because it has been calibrated using a certified reference material (CRM).

In the good manufacturing practice (GMP) world of the pharmaceutical industry, instrument qualification is part of the quality culture. Machines are checked, in some cases on a time basis, in other cases if anything at all has been changed, such as a column or pump part.

ISO/IEC 17025 is presently under revision and it seems that one of the changes will be to introduce a requirement for instrument qualification, in addition to method validation.

In exploring the differences between the ISO 17025 world and the GMP word, at least as far as this subject is concerned, I talked at length with Paul Boother, Operations Manager at Jaytee Biosciences Ltd. Jaytee know quite a lot about instrument validation. Paul and his colleague Annette Marshall put together a poster with me that was presented at the BERM 14 Conference held in October 2015 in the USA. I will be putting together a report on the Conference shortly and posting it on the *Spectroscopy Europe* web site.—PJ

Back to instrument qualification

It is now accepted universally, at least by readers of this column, that reliable analytical measurement underpins the chemical industry; whether in pharmaceutical manufacture, food safety or paint composition, the need to ensure product quality and safety is paramount.

Irrespective of the use of a quality standard, such as GMP or ISO 17025, failure to ensure valid analytical results can have massive impacts on an organisation and its reputation for product quality.

So, reliable measurement is the basis for all analytical techniques. As mentioned above, analysts spend a vast amount of time validating methods, running system suitability tests and performing QC and PT checks in order to demonstrate the validity of their results. All this work is based on the rationale that the instrument must be working correctly because all of the calibration, validation and QC checks have been done.

But what if the instrument itself was slightly faulty? The truth is that many methods are developed within ISO/IEC accredited laboratories using an instrument or instrument system which has never been qualified as working correctly since the time it was first installed in the laboratory, perhaps five years ago. Yes, a service engineer comes in once a year, but most service contracts only include a cursory check by the engineer after the annual service, not a full qualification against specification.

It is worth comparing the requirements of ISO/IEC 17025 and GMP:

GMP
"In Accordance with the cGMP regulations in 211.160 (b)(4), the analyst should ensure that only those instruments meeting established performance specifications are used and that all instruments are properly calibrated".[1]

ISO 17025:2005
Clause 5.5.2 states that "Equipment used for testing, calibration and sampling, shall be capable of achieving the accuracy required... It shall be checked and/or calibrated before use."[2]

The pharmaceutical industry requires a regime of regular instrument qualification, this combined with change control ensures that the equipment is "fit for purpose". But ISO/IEC 17025 (2005) only requires the equipment is checked or calibrated before use. The fundamental difference is "fitness for purpose".

How can this be proven? Let us take a specific example. A well-proven high-performance liquid chromatography system suffers a pump failure and the pump is replaced. At the same time a new column is fitted. So how can the user be sure that the instrument is still

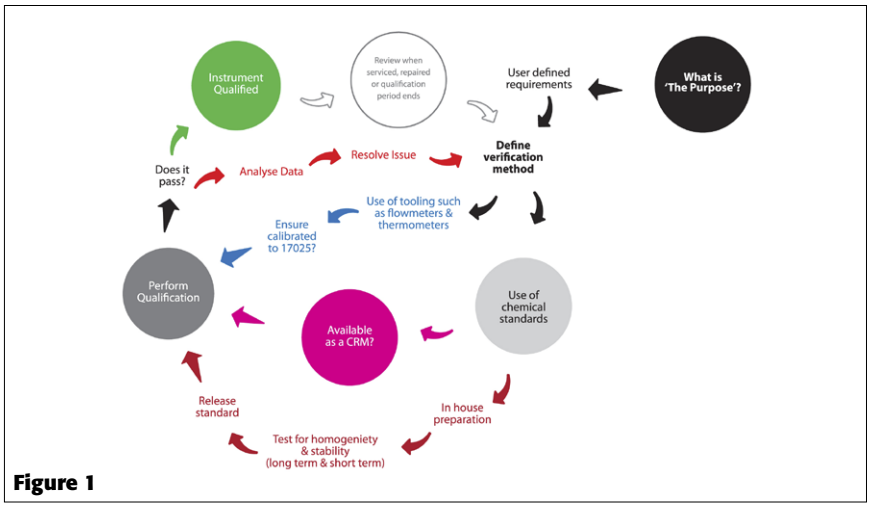


Figure 1

working, not just properly, but as it was previously? Any change in instrument performance may well bias the validated method running on the instrument. Figure 1 makes it clear that the procedure is not quick, or simple.

Another, common situation is that ongoing QA results are out of specification; typically the results have drifted outside the acceptable ±2SD range. It is all too easy to assume the problem is a standard, a reagent or the column when it may be something more fundamental. How can this be checked?

Figure 2 makes things clear. A machine that is working out of specification will frequently bias, in a reproducible way, a result, as shown in Figure 3.

Figure 3 demonstrates the impact of an unqualified instrument on the reported impurity level in a product: a simple wavelength fault is causing an impurity to be reported at a level far lower that the true amount. Wavelength faults will allow a

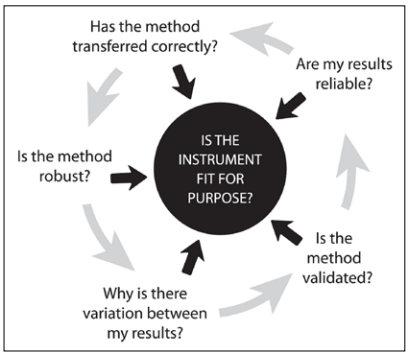


Figure 2

standard to be quantified, but because of the fault the standard has not been quantified at maximum absorbance, sensitivity is reduced. The result is that an impurity is not reported. Normal downstream rarely detects subtle errors of this type.

The risk is that data will be generated, but is not of usable quality. In USP Monograph <1058> on Analytical Instrument Qualification,[3] the concept of a Data Quality Triangle (DQT) is intro-

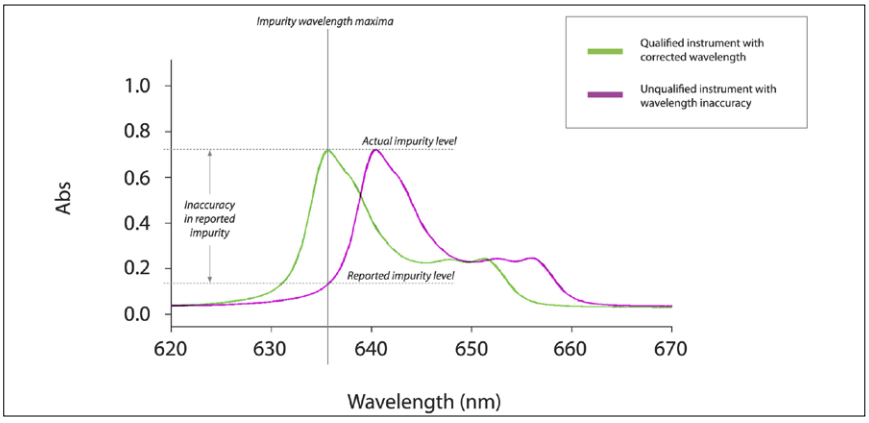
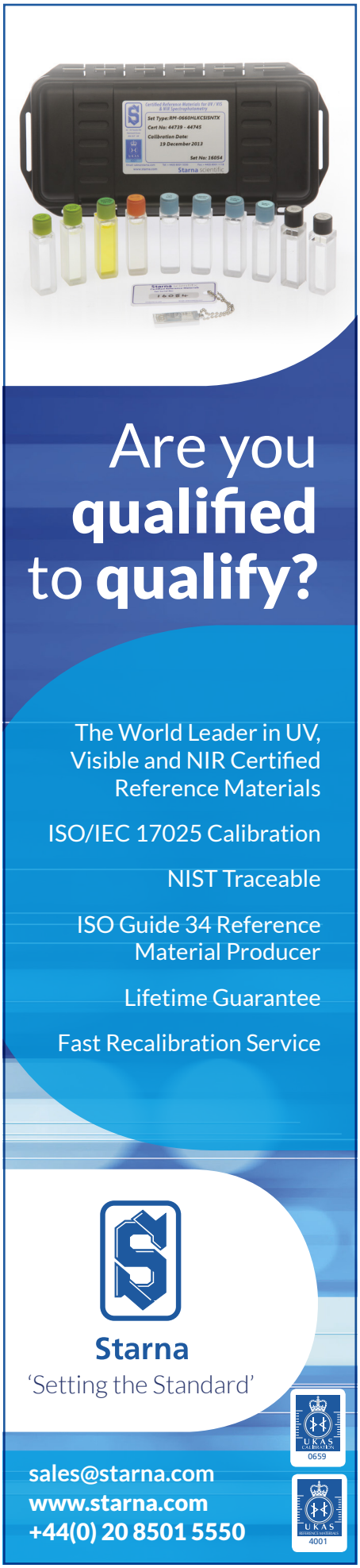


Figure 3



duced. The DQT clearly shows that instrument qualification is the foundation for all analytical data, as in all "triangle" models the lowest layer must be complete before the next layer is started (Figure 4).

Yet ISO/IEC 17025-2005 requires that all methods should be suitable and validated without demanding instrument qualification. So when ISO 17025 is implemented in the context of cGMP regulations, all equipment MUST undergo a regular performance qualification (PQ). But outside the cGMP arena no such PQ is mandated.

Instrument qualification should always be based on the intended use of the instrument or "purpose". This is part of the design qualification phase, which should be (but usually is not) carried out prior to the installation of the equipment.

Defining the purpose is vital for instrument qualification; there are countless examples of attempts to develop methods which exceed the capability if the instrument. One such example is expecting repeatability of less than 1% when the 15-year old instrument is only capable of less than 2%.

The term "not fit for purpose" is frequently used in laboratories the world over. This expression usually means

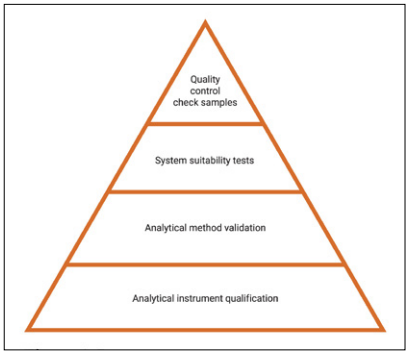


Figure 4

that it has not performed as the analyst expected. The questions that should reasonably be asked are how was the purpose defined and how has that been assessed?

Once the purpose has been established, the installation qualification (IQ) phase should be conducted followed by the operational qualification (OQ) phase. IQ is where the non-variable requirements of the "purpose" are reviewed; for example, has the instrument got the desired sample capacity? The OQ phase demonstrates that the instrument will operate as expected; e.g. no errors appear when the instrument is turned on.

Upon completion of the IQ/OQ phase the performance qualification (PQ) phase begins. This is where the instrument is qualified to ensure that it meets the requirements of the analysis being carried out in the laboratory. That is, running a CRM with certified wavelengths to prove that the instrument's wavelength is sufficiently accurate for the analysis that will be conducted. The benefit of using a CRM is that it provides instant traceability to the laboratory (Figure 5).

There are three basic rules:

- Qualification should always be based on simplicity!
- If complex chemistry is used to validate a complex instrumentation then any failure could be due to multiple factors and the true cause hidden!
- By simplifying the chemistry within the qualification process it is easy to see which failures are due to the instrumentation and which are from the method.

Unfortunately there are relatively few CRMs designed to qualify instruments, many laboratory managers see no need and produce their own, after all they are simple solutions, or are they? No, they are not. Increasingly, accreditation auditors look to see that in-house CRMs are produced so that they generally achieve the same quality level as a commercially produced CRM. Following ISO Guide 34, which is the "standard" for the production of CRMs, is complex and labour intensive as the list below makes clear.

- Chemicals and solvents required
- Methods to be developed and validated
- ISO Guide 34 Quality System to be maintained
- Homogeneity to be assessed
- Stability to be assessed
- Traceable links to international standards or NMIs to be established
- Equipment required to verify correct preparation
- Review by quality inspectors

As well as the time spent producing a CRM, the opportunity cost cannot be ignored. Essentially it is the value of the work that could have been done, and charged out by staff instead of preparing the "simple standard"!

Our advice is that whenever a CRM is available, use one! There are a number of reputable and fully accredited European suppliers who will help.

References

1. *Guidance for Industry, Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production*. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (October 2006). http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070287.pdf
2. EN ISO/IEC 17025:2005. http://www.iso.org/iso/catalogue_detail.htm?csnumber=39883
3. *USP 38, NF 33 <1058> Analytical Instrument Qualification*. http://www.usp.org/

User requirements specification	Qualification processes			Operation
				Quality control checks
Function specification	At installation (new, old or existing unqualified instrument)	After installation or major repair of each instrument	Periodically at specified intervals for each instrument	System suitability checks
Design specification				Calibration and maintenance
Design Qualification →	**Installation Qualification** →	**Operation Qualification** →	**Performance Qualification**	Performance Qualification
before installation		**before use**		**use**

Figure 5. Timeline of analytical instrumentation qualification (AIQ).