SPOTLIGHT feature

Reagents, Reference Materials & Laboratory Chemicals

Traceable Standards – The First Step towards Data Integrity

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In recent guidance [1], the UK's Medicines & Healthcare products Regulatory Agency (MHRA) observes that 'Data integrity is fundamental in a pharmaceutical quality system which ensures that medicines are of the required quality'. The US Food and Drug Administration (FDA) has recently issued a number of Warning Notices to pharmaceutical manufacturers that relate to Data Integrity failures – often to suppliers in the developing economies - and the EU Medicines Agencies Network Strategy to 2020 [2] has an objective to: 'Assure product supply chain and data integrity'.

Data Integrity is defined in MHRA guidance as 'The extent to which all data are complete, consistent and accurate throughout the data lifecycle', and of course this will be to a large extent be dependent on the way data is recorded, manipulated and stored, and regulations such as the FDA's 21 CFR Part 11 [3] are aimed at this area. The Organisation for Economic Co-operation and Development (OECD) consensus document 'The Application of the Principles of GLP to Computerised Systems' [4] is currently under review.

The data lifecycle, however, begins with the initial generation of the data, and as with any measurement process the old adage of "…garbage in, garbage out" is particularly appropriate; **so performance qualification of the analytical instrumentation used is fundamental to achieving overall data integrity**. It should be remembered that with most analytical instrumentation processes raw measurement data has its own internal data lifecycle, to a greater or lesser degree. The complexity of that data lifecycle will vary hugely depending on the type of equipment. In the case of stand-alone instruments measuring a single parameter, such as a balance or pH meter, it will probably be very simple. With more complex instrumentation such as HPLC, or certainly any kind of LIMS, it will be much more complex. UV spectrophotometry is one of the most widely used techniques in pharmaceutical analysis and quality control, and lies between these two extremes. Fortunately, there are well-established Certified Reference Materials (CRMs) for the qualification of UV spectrophotometers, and most regulatory bodies such as the pharmacopoeias give recommendations on the CRMs to be used for instrument qualification.

Analytical Instrument Qualification (AIQ)

Instrument qualification can be conveniently grouped into four phases: design qualification (DQ), installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ). All four phases must be documented and records kept. Good quality control procedures will also require that documented Standard Operating Procedures (SOPs) are employed and regular calibration is performed.

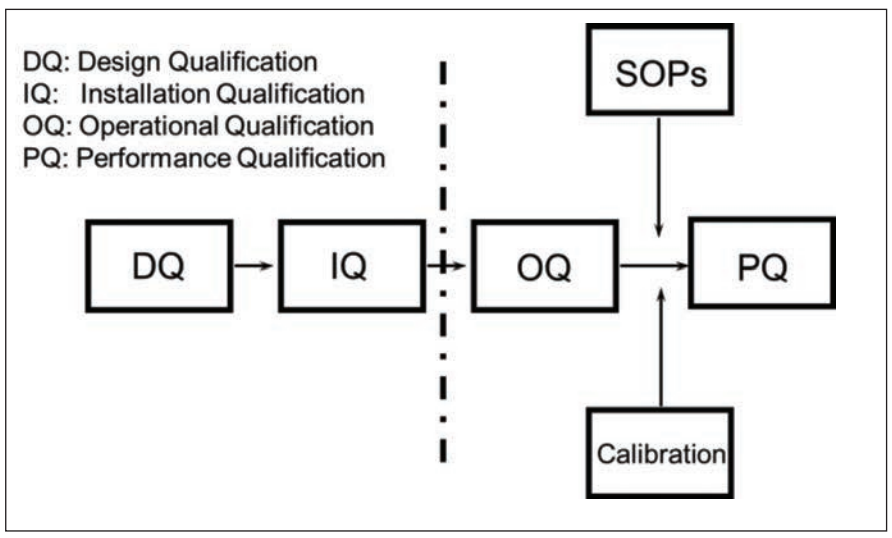

Figure 1. Analytical Instrument Qualification (AIQ)

DQ - Design Qualification: is the process that defines the functional and operational specifications of the instrument. It also provides the criteria by which users can select an instrument vendor, based on the intended application. The manufacturer is responsible for robust design and for maintaining information describing how the instrument is built and tested before shipment to users. Nevertheless, the user should ensure that commercial off-the-shelf instruments are suitable for their intended application, particularly in terms of the way raw data is handled, and whether there is an audit trail of that process. Many instrument designs incorporate some kind of internal calibration or 'self-test' routines, sometimes extending to automatic adjustment of the instrument. Users should ascertain whether these routines are traceable to recognised international standards, and whether they can be checked by reference to external CRMs.

IQ - Installation Qualification: establishes that an instrument is delivered as designed and specified, and is properly installed in the selected environment and that this environment is suitable for the instrument. IQ would also apply to a qualified instrument that has been transported to a new location or is being reinstalled for other reasons, such as prolonged storage.

OQ – Operational Qualification. Operational qualification (OQ) demonstrates that an instrument will function according to its operational specification and is suitable for the intended use and analytical procedures for which it is to be employed.

PQ – Performance Qualification: Performance qualification (PQ) is the documented collection of activities necessary to demonstrate that an instrument consistently performs according to the specifications defined by the user, and is appropriate for the intended use. After IQ and OQ have been performed, the instrument's continued suitability for its intended use is demonstrated through PQ.

Clearly, in a routine situation, only PQ may need to be performed on a regular basis, and OQ less frequently, for example after maintenance or repair operations have been carried out on the instrument.

In a regulated environment, the onus of proof is on the user to justify and prove, by the qualification of the system, that the instrument is 'fit for purpose' and capable of providing the required accuracy and precision of data.

AIQ does not prove that the analytical results generated by the spectrophotometer are correct! AIQ demonstrates that the instrument itself is working appropriately: many other factors, centred on the operative performing the measurement; for example, sampling procedures, reagent quality, sample handling, etc. contribute to the final result.

Certified Reference Materials – Can they Support Data Integrity?

As defined by ISO/REMCO (the International Standards Organisation Technical Committee on Reference Materials), a CRM is a

'Reference Material, characterised by a metrologically valid procedure for one or more specified properties, accompanied by a certificate that provides the value of the specified property, its associated uncertainty, and a statement of metrological traceability.'

If we intend to use a CRM to qualify a spectrophotometer as part of demonstrating overall data integrity, we must be able to quantify the measurement uncertainty of the certified values of the CRM and demonstrate traceability.

The preparation of a typical CRM could be subject to many variables, and establishing the uncertainty of the final assigned measurement value can be complicated [5]. From the user's point of view, it is far simpler to purchase Certified Reference Materials from an accredited Reference Material Producer, than to prepare, values assign, and calculate the related associated expanded uncertainty budget. By definition, an accredited Reference Material producer will have prepared and certified the CRMs under closely controlled conditions, which will be accompanied by a certificate in which the measurement uncertainty will be stated. The usual convention is to state an 'uncertainty budget' with a confidence level of 95%, i.e. k=2.

Traceability is another very important concept in the qualification process, defined in ISO/IEC Guide 99:2007 as the '**property of a measurement result whereby the result can be related to a reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty**'. This means that the reference spectrophotometers used to establish the certified values must themselves be qualified using Standard Reference Materials certified by National Metrology Institutes such as the National Institute of Standards and Technology (NIST) in the USA, or against primary physical references such as elemental emission lines.

This fundamental concept in comprehensively reviewed in Technical Report from ISO/REMCO, to be published shortly [6].

To be a Reference Material Producer, manufacturers should be accredited to ISO Guide 34, a revised version of which is soon to be issued as ISO 17034. This standard contains normative references to ISO/IEC 17025, so that the certified value assignments must only be produced in calibration laboratories accredited to this standard also. When assessing a reference material producer, it is important to consider the scope of their accreditation: a supplier could claim accreditation to Guide 34 or ISO/IEC 17025 based on just one type of reference material, **which might not be the one to be purchased**. References not included in the published scope may not be recognised for instrument qualification by the regulatory bodies. Potential purchasers can establish the scope of a supplier's accreditation by referring to the appropriate National Accreditation Body, a comprehensive list of which can be found on the International Laboratory Accreditation Cooperation (ILAC) website (www.ilac.org).

My Spectrophotometer is Pharmacopoeia Compliant – is that good enough?

Much pharmaceutical analysis is performed using methods issued by the various Pharmacopoeias, who set their own criteria for instrument qualification. Specifications are published for absorbance accuracy and linearity, wavelength calibration and spectral bandwidth, and sets of reference materials are available commercially to qualify instruments to these criteria.

Figure 2 - Typical set of Certified Reference Materials for Pharmacopoeia Compliance

While the pharmacopoeias and other standards may give generic recommendations for instrument qualification, for some applications the required performance characteristics may lie outside the scope of the recommended CRMs and in this case the user may have to look for other reference materials with which to qualify the instrument. Compliance to a given standard does not necessarily mean 'best practice' and a user should set appropriate performance standards for their own application. It should be remembered that in a regulated environment, the onus of proof is on the user to justify and prove that the instrument is 'fit for purpose' over the operational ranges required within the laboratory, which forms the fundamental requirement of the PQ.

For example, both the US and European Pharmacopoeia recommend potassium dichromate solutions for qualifying absorbance accuracy. The usable wavelength range of this solution is from 235 to 430 nm.

'What if your analytical measurement wavelength lies outside this range, and therefore ideally qualification wavelengths should 'bracket' the analytical wavelength?'

Fortunately, several references have been developed, some proprietary, which cover virtually the entire UV/visible spectrum:

Reference Material	Usable Range (nm)
Starna Deep UV (DUV)	190 – 230
Nicotinic acid solution	210 – 260
Potassium dichromate solution	235 - 430
Starna Green solution	250 - 650
Neutral density filters	440 - 635
Metal-on-quartz filters	250 - 2500

Similarly, for wavelength qualification, the recommended reference material is holmium oxide solution. This has a usable range from 240 nm to 650 nm. Again, a whole series of reference materials allow instrument qualification outside these limits:

Reference Material	Usable Range (nm)
Starna Deep UV (DUV)	190 – 230
Starna 'Rare Earth' solution	200 - 270
Samarium perchlorate	230 - 500
Didymium oxide	290 - 870
Starna NearIR (NIR) reference	930 - 2550

As stated earlier, the measured value of a CRM on a given spectrophotometer may also be highly dependent on user controlled parameters, and within these variables, one can specifically state the physical controls of instrumental spectral bandwidth and temperature.

Whilst the acceptable limits/range for these physical parameters should be specified on the certification of the CRM, these criteria are sometimes not appreciated, and/or adhered to, and as a consequence 'incorrect' values may be reported?

Whilst an accredited Reference Material Producer may not be able to provide certified values under customer-specified operating conditions relating to the above, they should be capable of providing information values, within the measurement capability of their laboratory.

Conclusions

Instrument Qualification is the first step towards achieving Data Integrity in spectrophotometric pharmaceutical analysis. In many situations, the Certified Reference Materials recommended by Pharmacopoeias and other regulatory bodies can provide the DQ specified OQ in the qualification cycle. However, there will be the laboratory specific, additional OQ/PQ requirements where these references may not be fully appropriate for the analytical procedure in use; because they do not cover the appropriate wavelength and/or Absorbance range(s), etc. Many other reference materials have been developed to address such a scenario, and in relation to this requirement the position of regulatory authorities is clear: whilst the user cannot be expected to go to unreasonable lengths to prove fitness for purpose, if suitable CRMs are available they should be used. Failure to use any available CRMs would be deemed to be a breach of compliance, with the related potential serious consequences!

References

1. *GMP Data Integrity Definitions and Guidance for Industry – UK Medical & Healthcare Regulatory Authority/ March 2015*
2. *EU Medicines Agencies Network Strategy to 2020 – European Medicines Agency. March 2015*
3. *FDA Regulation 21 CFR Part 11 - Electronic Records; Electronic Signatures (2003)*
4. *Application of the Principles of GLP to Computerised Systems. OECD Environment monograph no 116, 1995.*
5. *Burgess, C: Measurement Uncertainty without the Math. Pharmaceutical Technology, Feb 2016.*
6. *ISO TR-16476:2016 – Reference Materials-Establishing and expressing metrological traceability & quantity values assigned to reference materials.*