# The qualification and validation of near infrared spectrometry systems: issues and practical approaches

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## Defining the NIR system

One of the key requirements for regulatory compliance is that the system is completely defined. Figure 1 shows the components which comprise a typical system. At the heart of the system is the spectrometer itself. However, this is only part of the whole system. The computer system which controls it has both hardware and software components which need to be validated. All accessories associated with the sample presentation and handling need to be defined and qualified. Most importantly, the operators need to be trained and standard operating procedures written.

## Qualification and validation

There is a great deal of confusion regarding the use of these terms. My recommendation is to use the term 'validation' when we are looking at a system and to use the word 'qualification' when we are looking at an individual instrument or component. Qualification includes calibration and standardisation aspects for individual instruments or components. The regulations are not always clear and tend to apply 'validation' as an all embracing term. The focus of this paper is on the qualification of the spectrometer.

ISO Guide 9001, section 4.11, gives clear guidance on the requirements for calibrating analytical equipment: "...the user shall identify, calibrate and adjust all inspection, measuring and test equipment and devices that can affect product quality at prescribed intervals, or prior to use, against certified equipment having a known valid relationship to nationally recognised standards."

However, this does not cover the broader aspects of qualification nor validation of the overall system. The Code of Federal Regulations (CFR) in the USA, on the other, hand goes further in requiring scientific soundness, written instrument requirements and a specific requirement that if these are not met then they must not be used.

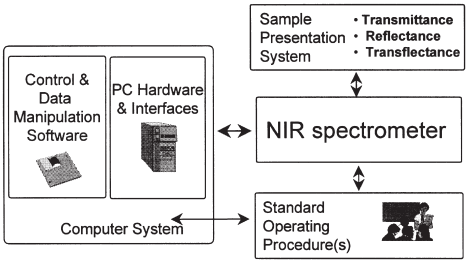


**Figure 1. Components of a computerised NIR system.**

§ 211.160 General requirements

*(b) Laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling and*

drug products conform to appropriate standards of identity, strength, quality and purity. Laboratory controls shall include:

*(4) The calibration of instruments, apparatus, gauges and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision and provisions for remedial action in the event accuracy and/or precision limits are not met. Instruments, apparatus, gauges, and recording devices not meeting established specifications shall not be used.*"

For computerised systems, validation is required. Annex 11 of the *European Guide to GMP* requires that: "*Validation should be considered as part of the complete life cycle of a computer system. This cycle includes the stages of planning, specification, programming, testing, commissioning, documentation, operation, monitoring and modifying.*

*The extent of validation necessary will depend on a number of factors including the use to which the system is to be put, whether the validation is to be prospective or retrospective and whether or not novel elements are incorporated.*"

Note that the extent of the software testing required is dependent on the use to which the system is put. The CFR is more explicit in requiring calculation integrity to be established.

### §211.68 Automatic, mechanical, and electronic equipment

*(b) Input to and output from the computer or related system of formulas or other records or data shall be checked for accuracy. The degree and frequency of input/output verification shall be based on the complexity and reliability of the computer or related system.*"

## Approaches to establishing integrity of analytical results

The 'bottom up' approach is the most logical. Like 'Lego', the quality of the end result is built in from the foundations up. In testing terms this is illustrated in Figure 2. These 'Lego' bricks are equivalent to the individual modules in any measurement system. Each brick is qualified as suitable for use before the next layer is built. In this way, integrity is assured all the way to the top-most layer. If firm foundations are not built, the information generated will not stand scrutiny. By following this approach, quality is built in from the lowest level.

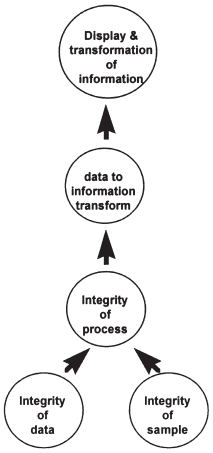


**Figure 2. The 'bottom up' approach to data integrity.**

The role of the instrument in providing the integrity of data is fundamental to the end result. If you cannot place your faith in the reliability of the basic analytical signal within predetermined limits then the information generated will be worse than useless. The reliability of the data quality should be linked to performance standards for both modules and systems as well as having a regular maintenance programme.

This paper is only focusing on the integrity of the analytical data aspect of the spectrometer's performance. For more details on equipment qualification see References 1–3.

## Requirements of the *European Pharmacopoeia*

The *European Pharmacopoeia*, 3rd Edition, has specific requirements for NIR spectrometry in Section 2.2.40. The requirements relating to the control of the instrument are listed below.

### Verification of the wavelength scale (except for filter apparatus)

Verify the wavelength scale employed, generally in the region between 780 nm and 2500 nm using (a) suitable wavelength standard(s) which has

characteristic maxima at the wavelengths under investigation, for example polystyrene or rare-earth oxides.

### Verification of the wavelength repeatability (except for filter apparatus)

Verify the wavelength repeatability using (a) suitable standard(s), for example, polystyrene or rare-earth oxides. The standard deviation of the wavelengths is consistent with the spectrophotometer specification.

### Verification of response repeatability

Verify the response repeatability using (a) suitable standard(s), for example, reflective thermoplastic resins doped with carbon black. The standard deviation of the maximum response is consistent with the spectrophotometer specification.

### Verification of photometric noise

Determine the photometric noise using a suitable reflectance standard, for example, white reflective ceramic tiles or reflective thermoplastic resins. Scan the reflection standard in accordance with the spectrophotometer manufacturer's recommendation and calculate the photometric noise, either peak to peak, or for a given wavelength. In the latter case, the photometric noise is represented by the standard deviation of the responses. The photometric noise is consistent with the spectrophotometer specification.

The *European Pharmacopoeia* regulatory requirement for NIR instrument performance and control is clearly stated as compliance with the manufacturer's specification.

## Requirements of the *United States Pharmacopoeia*

The *United States Pharmacopoeia 24* has specific requirements for NIR spectrometry in Section <1119> currently in draft.[4] "Instrument qualification is to assure that an instrument is suitable for its intended application and, when periodically requalified, it continues to function properly over extended time periods".

This instrument qualification needs to be carried out every six months or following repair or optical reconfiguration. In addition, performance verification is required to assure that the instrument system has not suffered wavelength shifts or sensitivity changes whilst in routine operation. Performance verification is to be carried out on a monthly basis on instruments configured for measurement for wavelength accuracy, absorbance/reflectance scale linearity and high light level noise. Performance verification is consistent with the holistic testing approach for complex analytical systems, for example, chromatographic systems proposed by the Food & Drug Administration, USA.[5] The recommended performance specifications relating to the performance verification of the instrument are listed in .

This approach, which does not rely solely on compliance with the manufacturer's specification, is in accordance with the 4 'Q's model discussed later. It goes much further than the *European Pharmacopoeia* in setting performance standards and methods of test.

### Requirements of the American Society for Testing and Materials (ASTM)

Although not a regulatory body in the same way as the FDA or the Pharmacopeias, the American Society for Testing and Materials (ASTM) is a very important and widely recognised organisation whose standards of instrument performance are widely adopted by instrument manufacturers.

These tests are designed as rapid, routine checks of spectrophotometer performance to uncover malfunctions or other changes in instrument operation. They are not intended for comparison of spectrophotometers of different manufacture. Currently, there are no standards relating to reflectance in-

struments. Three of the relevant standards are: E275—Practice for describing and measuring performance of ultraviolet visible and near infrared spectrophotometers; E 925—Practice for the periodic calibration of narrow band-pass spectrophotometers; E1866—Standard guide for establishing spectrophotometer performance tests.

## The 4 'Q's model as an approach to the qualification of NIR spectrometry systems

The Pharmaceutical industry has adopted an approach to equipment qualification which has become known as the 4Q's model: **D**esign **Q**ualification (DQ), **I**nstallation **Q**ualification (IQ), **O**perational **Q**ualification (OQ) and **P**erformance **Q**ualification (PQ).

The Pharmaceutical Analytical Science Group (PASG),[6] have produced a position paper on equipment qualification in which they proposed the following definitions of the 4qs. DQ: Defining the quality parameters that the required of the equipment and manufacturer. IQ: assurance that the intended equipment is received as designed and specified. OQ: confirmation that the equipment functions as specified and operates correctly. PQ: confirmation that the equipment consistently continues to perform as required.

These definitions are consistent with those recently published by the Eurachem-UK Instrumentation Working Group[7] and Pharmaceutical Inspection Convention (PIC) .

There is, however, one difficulty with this nomenclature. A modified form of the 4Qs model is used for validation of computerised systems. Here the same terms are used as equipment qualification, unfortunately they have a different meaning.[8]

- User Requirements Specification (URS) is equivalent to the design qualification
- IQ: documented verification that all key aspects of hardware installation adhere to appropriate codes and approved design intentions and recommendations of the manufacturer have been suitably considered. (In practice this means ensuring that the system is installed as specified and sufficient documented evidence exists to demonstrate this.).
- OQ: documented verification that the equipment or system operated as intended throughout require or anticipated operating ranges. (In practice this means works as specified and sufficient documented evidence exists to demonstrate this)

**Table 1. USP24 <1119> recommended NIR instrument specifications.[a]**

| | |
|---|---|
| Wavelength uncertainty | SRM 1920[a] peaks[b] occur at 1261, 1681 and 1935 nm<br>± 1 nm at 1200 nm or ± 8 $cm^{-1}$ at 8300 $cm^{-1}$ |
| Tolerances | ±1 nm at 1600 nm or ± 4 $cm^{-1}$ at 6250 $cm^{-1}$<br>± 1.5 nm at 2000 nm or ± 4 $cm^{-1}$ at 5000 $cm^{-1}$ |
| Noise<br><br>Average RMS for measurements at high light flux<br><br>Average RMS for measurements at low light flux | Measured for 100 nm (300 $cm^{-1}$) segments between 1200 and 2200 nm (8300 and 4500 $cm^{-1}$)<br>$< 0.3 \times 10^{-3}$,<br>no RMS $> 0.8 \times 10^{-3}$<br>$< 1 \times 10^{-3}$,<br>no RMS $> 2.0 \times 10^{-3}$ |
| Photometric linearity | $A_{OBS}$ vs $A_{REF}$ at 1200, 1600 and 2000 nm[c]<br>Slope = 1.0 ± 0.05; intercept = 0 ± 0.05 |

[a]A maximum nominal instrument bandwidth of 10 nm at 2500 nm or 16 $cm^{-1}$ at 4000 $cm^{-1}$ is appropriate for most applications. [B] The nominal 1935 nm peak is sensitive to instrument band width. Use the wavelength value supplied with SRM 1920[a] at the appropriate instrument band width to determine wavelength uncertainly. [c]$A_{OBS}$ is the observed absorbance and $A_{REF}$ is the tabulated absorbance of the reference reflectors at each of the three specified wavelengths

- PQ: documented verification that the system performs as intended throughout all anticipated operating ranges. (In practice ensuring the system in normal operating environment produces an acceptable quality product and sufficient documented evidence exists to demonstrate this.)

Thus, in computerised system validation, there is an additional stage before the system can be released for operational use. These differences in terminology can be very confusing for those analytical scientists involved in both equipment qualification and computerised system validation. The nomenclature overlap is pictorially represented in Figure 4. In the case of NIR systems both nomenclatures are applicable and care has to be taken with definitions.

## Key parameters for qualification of NIR spectrometers

Currently, there are over 50 manufacturers and over 100 different models of NIR spectrometers in the market place. They include the following instrument types and sampling accessories: Filter, Dispersive, FT interferometers, AOTF (Acousto-Optical Tuneable Filter), Diode array, ATR (Attenuated Total Reflectance), Fibre optics probes with many different designs and Integrating spheres. Which may be operating in transmittance, reflectance, specular and diffuse and transflectance modes.

Not surprisingly, there is no uniformity of specification by manufacturers. Indeed, some manufacturers will not publish or disclose performance measures. There is much confusion over the meaning of terms leading to great difficulty in comparing instruments and setting meaningful performance criteria. The approach, as taken by the *European Pharmacopoeia*, is not helped by these inconsistencies. The USP approach is preferred as it encompasses both the compliance with manufacturer's specification and traceable standards with acceptance criteria which are independent of the equipment. Even so the current requirements of USP <1119> are not comprehensive and do not include requirements for spectral bandwidth, drift or stray light.

Ideally, the parameters that need to be controlled are: Wavelength accuracy and reproducibility, Photometric scale linearity, Noise, Drift, Spectral bandwidth and Stray light. For wavelength accuracy and reproducibility, standard materials traceable to NIST (National Institute of Science and Technology, USA) or NPL (National Physical Laboratory, UK) are readily available for transmittance, reflectance and transflectance. These are summarised in Table 2.

There are currently no commercially available traceable wavelength standards for the region 2000 to 2500 nm. The spectrum of crystalline polystyrene has four bands, at approximately 1144 nm, 1680 nm, 2167 nm and 2307 nm.[9] NPL and NIST can carry out a custom calibration service if required.

- ❑ **Design Qualification**
  - ● What do you want the instrument/system to do?
  - ☺ Setting 'suitability for use' criteria to meet business needs
- ❑ **Installation Qualification**
  - ● Does the instrument/system work the way manufacturers say it should?
  - ☺ *Compliance with specification*
- ❑ **Operational Qualification**
  - ● Does the instrument work for your specific applications?
  - ☺ *Operability in your environment*
- ❑ **Performance Qualification**
  - ● Does the instrument continue to work in the matter intended?
  - ☺ Ongoing compliance

**Figure 3. 4 'Q's model for instrument qualification**

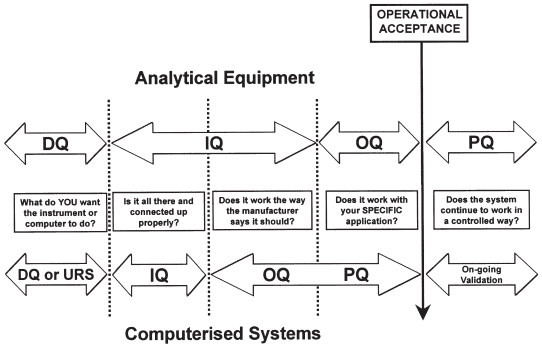


**Figure 4. Comparison of the 4'Q's models for equipment qualification and computerised system validation.**

The qualification of the linearity of the photometric scale is also a practical proposition using traceable standards. Materials are available for transmittance and reflectance. Table 3 gives a listing of available standards.

The current requirement is for linearity only and not accuracy, although this is implied in linearity of <1119> requirements. However, if data transfer between instruments is required, the accuracy of the both the wavelength and photometric scales has to be known.

Although the USP has requirements for RMS noise, there is currently no standard agreed approach to the measurement of noise and drift. ASTM E 1866-97 provides a method for determination of RMS of short term noise but emphasises that the test is not intended for the purpose of comparing spectrophotometers of different manufacture! ASTM E 1657-94 on testing variable wavelength photometric detectors used in liquid chromatography provides a method for determination of short term noise, long term noise and drift. This approach, for the basis of testing of NIR spectrometers, is illustrated in Figure 5.

The effects of spectral bandwidth (SBW) and stray light have not been well explored in the NIR. However, Norris[10] has shown that there are important interactions between SBW, instrument noise and the natural bandwidth of the sample. These interactions also affect the calibration function and have implications for smoothing. Dispersive instruments, traditionally, have a large SBW (8 nm+) for ex-

**Table 2. Standards for wavelength calibration of NIR spectrometers.**

| MODE | MATERIAL | SOURCE |
|---|---|---|
| Transmittance | Polystyrene | NPL |
| | | NIST SRM 1921 |
| | YAG laser crystal materials | NPL; 868.7 nm, 1485.9 nm and 1735.0 nm |
| Reflectance | Polystyrene | NPL |
| | YAG laser crystal materials with white reflector | NPL; 868.7 nm, 1485.9 nm and 1735.0 nm |
| | rare earth oxides | NIST SRM 1920a; 740 to 2000 nm |
| Transflectance | Rare earth oxide in glass | NIST SRM 2035; 971 nm to 1949 nm |

**Table 3. Standards for photometric scale calibration of NIR spectrometers.**

| MODE | MATERIAL/GEOMETRY | SOURCE |
|---|---|---|
| Transmittance | Schott NG series glass filters | NPL |
| | Metal on quartz filters | NPL or NIST |
| Reflectance | | |
| Specular | | NIST SRM 2003, 2011, 2023 & 2026 |
| Diffuse | 6° / hemispherical | NIST SRM 2015 |
| | Calibrated carbon doped Spectralon™ | NPL or NIST |

cellent signal-to-noise ratios as NIR bands were considered broad and relatively featureless. This has lead to the idea that SBW is not particularly important in the NIR. However, modern FT instruments allow a much smaller SBW to be employed, i.e. 2 nm or less. In these circumstances the measurement of the observed half bandwidth of a suitable atomic line would be applicable, as is done in the visible region with the 656 nm deuterium line.[11]

As with noise and drift there is no agreed approach for the determination of Stray light. ASTM E 387 has a method for transmittance spectrometers but does not have a suitable filter for the NIR. The Fleming–Mielenz method would be applicable if a suitably strong isolated NIR absorption band was available.

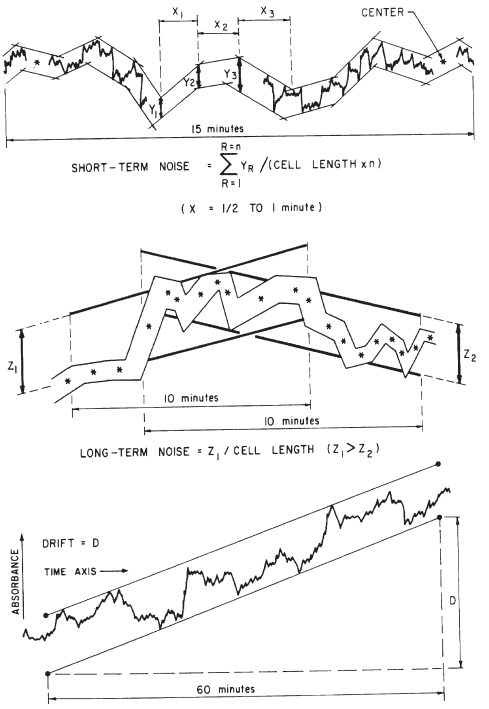


**Figure 5. ASTM method E1657-94 approach to the measurement of noise and drift.**

## Summary and conclusions

The qualification and validation of NIR spectrometry systems is a requirement for regulated industries. The framework for meeting these requirements is now better understood and has been reviewed. Some of the issues around calibration and performance monitoring have been discussed. Developments in calibration methodology and availability of new transfer standards are required in order to ensure 'fitness for purpose' and transferability of calibrations and methods.

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