Validation of NIR methods for pharmaceutical analyses

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Introduction

The global pharmaceutical industry is a heavily regulated one to ensure that medicines are safe, efficacious and of the correct quality. Regulatory agencies such as the Food and Drugs Administration (FDA) in the USA and the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK exist to regulate the industry, and pharmacopoeias such as the United States Pharmacopeia (USP) and the European Pharmacopoeia (EP) also lay down quality standards for medicines.

The pharmaceutical industry may have initial difficulties in developing and using near-infrared (NIR) methods because the product physical characteristics may not have been finalised. There may also be problems later with the scale-up of the manufacturing process and changes in the suppliers of the excipients. This contribution gives an overview of the validation requirements for NIR methods in pharmaceutical analyses.

Application requirements

Applications for marketing authorisation, or variations to an existing authorisation, involving the use of NIR spectroscopy should include a clear protocol defining the application from beginning to the end. There should be a brief discussion on the theory of NIR spectroscopy, instrument optimisation and validation of the instrument(s) and software used.

Information required

The following types of details would be expected in a quantitative application:

- Instrument
- Software
- Data pre-treatment
- Calibration sets
- Method of optimising the calibration equation
- Sampling
- Reference spectra
- Validation information

Validation is all about demonstrating that the final method is fit for purpose. There are issues that have been identified by regulatory agencies and some of these are given below:

- A primary reference method should be available
- The contribution to the model by changes in physical parameters should be understood
- Is the method transferable between different NIR instruments?
- Is the method transferable between different software packages?
- What happens if the process or raw material supplier changes?
- The concept of compliance is probably acceptable

Near Infrared Spectroscopy: Proceedings of the 11th International Conference.
www.nirpublications.com

Compliance

At the moment, the industry buys raw materials from excipient manufacturers according to preset specifications and then a certificate of analysis is obtained to demonstrate that a given batch matches the specification and is therefore fit for purpose. In the future, a certificate of analysis may just say that the material conforms to various parameters such as identity, moisture etc rather than giving particular numbers.

Validation guidelines

The International Conference on Harmonisation (ICH) was set up to develop guidelines for the documentation for applications for marketing authorisation that would be applicable globally and be acceptable to the regulatory authorities in the USA, Japan and Europe. One guideline was for the Validation of Analytical Procedures[1] which was later supplemented by a further guideline giving a discussion on the characteristics that should be considered.[2] Both the USP[3] and the EP[4] have general monographs on the use of NIR spectroscopy and both are in the process of being updated.[5,6]

For identification of raw materials by NIR, batches showing the variation typically expected (and acceptable) should be used, eg different particle sizes and physical forms. Libraries should then be created that have the same:

- Spectral range and number of sample points
- Technique of measurement
- Data pre-treatment

The library should then be challenged with independent samples to validate it.

The ICH guidelines for quantitative methods were written with separative methods such as high-performance liquid chromatography (HPLC) in mind. However, non-separative methods such as NIR spectroscopy can meet the requirements of the guidelines and each characteristic of the ICH Validation Guidelines is given below using a published assay of paracetamol in an intact tablet as an example.[7]

Specificity

Spectra could be run for the active and all other relevant substances to show that there is a lack of interference in the assay from excipients etc. Alternatively, possible interfering compounds could be added to the tablet matrix to show non-interference. A further way is to demonstrate a linear relationship between concentrations of active and NIR values which would show that there is no interference in the assay.

If there are problems with the specificity of the assay, it may be improved by using data pre-treatment techniques or by using the complete spectral information available using techniques such as principal components regression (PCR) or partial least-squares regression (PLSR).

Linearity

A straight-line calibration over the working range of the assay should be shown. This is normally a plot of NIR predicted assay values against reference values when using multi-dimensional models and calibrations. Linearity can be evaluated from the correlation coefficient, y-intercept and slope of the regression line.

Range

A basic philosophy is to use a calibration range that is twice the permitted range. For example, pharmacopoeias permit a range of ± 5% of the nominal value to accommodate variations in production, degradation over the shelf-life of the product and accuracy of the assay; so that an assay range of ± 10% would be suitable.

However, it would be better to use ± 20% if that could be achieved. For content uniformity purposes, the range would have to be increased to something like ± 30%.

Accuracy

In NIR assays the accuracy is often given by reference to the Standard Error of Calibration (SEC) and Standard Error of Prediction (SEP). When trying to compare different NIR assays it is more convenient to use the Relative Standard Error of Prediction (%RSEP). Figure 1 is a plot of %RSEP vs concentration of active for a number of published assays of actives in intact pharmaceutical products. It clearly shows that the %RSEP increases as the concentration of active decreases and below about 20 %m/m the %RSEP rises very steeply from about 1 % to 8 %. Transmittance measurements appear to be more popular below 20 %m/m and are also more accurate than reflectance measurements at low concentrations of actives.

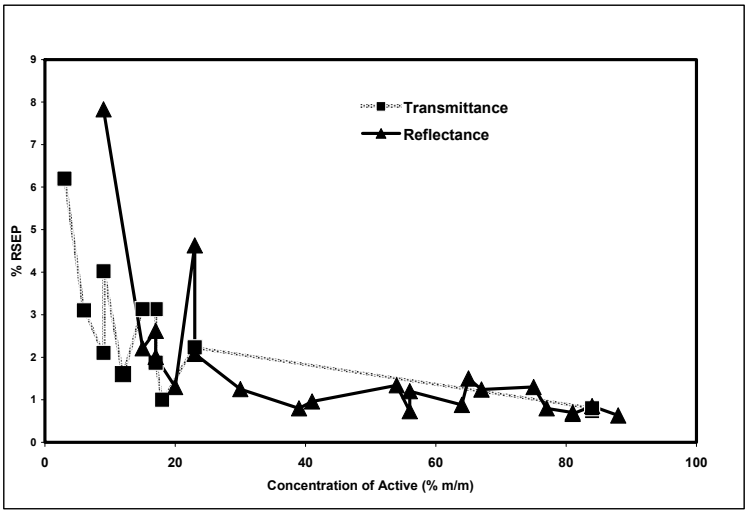

Figure1. Change of %RSEP with concentration of active (%m/m) in published NIR assays of actives in intact pharmaceutical preparations.

Whilst the calibration is made using a calibration set of samples, the validation is made using a second, independent set of samples. A further, separate set of samples collected at a later date can add to the validation by showing that the assay is robust over time. The assay of paracetamol in intact tablets by releflectance NIR spectroscopy is an example of an accurate assay where the standard errors for the calibration, validation and parallel test sets were 0.48 %m/m, 0.71 %m/m and 0.53 %m/m respectively for a paracetamol content of 84.18 %m/m.[7]

Precision

The repeatability (short-term or intra-assay precision) may be measured using six measurements on the same sample on the same day. Intermediate precision (between-day or inter-assay precision) can be measured using a single sample measured on separate days. Finally, the reproducibility of NIR assays is a measure of the between laboratory precision normally achieved by an inter-laboratory trial. Unfortunately there are very few of these that have been published.

Detection limit

This characteristic is not required for validating assays.

Quantitation limit

This characteristic is not required for validating assays.

Robustness

Typical challenges for measurements are changes of:

- Temperature
- Moisture and solvent residues
- Sample thickness
- Sample compression (for powders)
- Polymorphism and crystallinity
- Particle size
- Age of samples

System suitability tests

These are generally set by the manufacture and such tests are normally built into the software. However the following should be tested:

- Wavelength accuracy
- Wavelength repeatability
- Photometric linearity
- Response stability
- Photometric noise

Ongoing model evaluation

It is widely recognised that a model must be continuously evaluated (and improved where possible). This is because the samples being received or produced may change over time or the manufacturing process itself may change. Whilst these differences may not be detected by purely chemical methods such as HPLC, they are very likely to be picked up by NIR methods and so continuous monitoring of the model is necessary. A qualitative model should be revalidated when there are:

- Additions to the library
- Changes to the physical properties of a material
- Changes in the source of supply
- Wider range of material characteristics

Quantitative methods should be revalidated when there are changes in:

- Composition of the finished product
- Manufacturing process
- Sources or grades of the raw materials

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