for any analytical procedure. Specific acceptance criteria for each validation parameter must be consistent with the intended use of the method.

Specificity. The relative discriminatory power and selectivity for quantitative determination must be similar to those mentioned under Qualitative analysis. The extent of specificity testing is dependent on the application and the risks being controlled. Variations in matrix concentrations within the operating range of the method must not affect the quantitative measurement significantly.

Linearity. The validation of linearity involves the correlation of NIR results calculated from NIR responses within the used algorithms to reference method results distributed throughout the defined range of the calibration model. Actual NIR responses that are non-linear may still be valid.

Range. The range of analyte reference values defines the range of the NIR method and quantitation limits of the method. Controls must be in place to ensure that results outside the validated range are not accepted.

Accuracy. This can be determined by comparison with the validation method or with known samples (samples of blank and added amounts of tested substance). Accuracy can be indicated by the standard error of prediction (SEP) of the NIR method that should be in close agreement with the data of the validated method. The SEP is the standard deviation of the residuals obtained from comparing the NIR results with analytical reference data for the specified samples. It is demonstrated by correlation of NIR results with analytical reference data, by comparison of the SEP to the reference method used for validation. Alternatively statistical comparison methods may be used to compare NIR results with reference values (paired t-test, bias evaluation).

Precision. This expresses the closeness of agreement between a series of measurements under the prescribed conditions. It is assessed by a minimum of 6 measurements performed according to the developed analytical method. Precision may be considered at 2 levels, repeatability (replicate measurements of the same sample with or without variation in sample positioning) and intermediate precision (replicate measurements by different analysts, different days of measurements).

Robustness. This includes the effects of variations of temperature, humidity, sample handling and the influence of instrument changes.

Outliers. Outlier results from NIR measurements of a sample containing an analyte outside the calibration range indicates that further testing is required. If further testing of the sample by an appropriate analytical method gives the analyte content within the specifications, this may be accepted and considered to have met the specifications. Thus an outlier result generated by NIR measurements of the sample may still meet specifications for the analyte of interest.

ONGOING MODEL EVALUATION

NIR models validated for use are subjected to ongoing performance evaluation and monitoring of validation parameters. If discrepancies are found, corrective action will be necessary. The degree of revalidation required depends on the nature of the changes. Revalidation of a qualitative model will be necessary when a new material is added to the reference library and may be necessary when changes in the physical properties of the material occur and when changes in the source of supply take place. Revalidation of a quantitative model is required on account of changes in the composition of the finished product, in the manufacturing process and in sources/grades of raw materials.

TRANSFER OF DATABASES

When databases are transferred to another instrument, spectral range, number of data points, spectral resolution and other parameters have to be taken into consideration. Further procedures and criteria must be applied to demonstrate that the model remains valid with the new database or new instrument.

DATA STORAGE

Store the electronic NIR spectra, libraries and data according to the current regulations.

Store the NIR spectra with the necessary data pre-treatment for the special use (for example identification, particle size analysis, content of water etc.) according to the current specifications.

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2.2.41. CIRCULAR DICHLORISM

The difference in absorbance of optically active substances within an absorption band for left and right circularly polarised light is referred to as circular dichroism.

Direct measurement gives a mean algebraic value:

\[ \Delta A = A_L - A_R \]

\( \Delta A \) = circular dichroic absorbance,

\( A_L \) = absorbance of left circularly polarised light,

\( A_R \) = absorbance of right circularly polarised light.

Circular dichroism is calculated using the equation:

\[ \Delta \varepsilon = \varepsilon_L - \varepsilon_R = \frac{\Delta A}{\varepsilon \times l} \]

\( \Delta \varepsilon \) = molar circular dichroism or molar differential dichroic absorbptivity expressed in litre\(\text{mole}^{-1}\text{cm}^{-1}\),

\( \varepsilon_L \) = molar absorptivity (2.2.25) of left circularly polarised light,

\( \varepsilon_R \) = molar absorptivity of right circularly polarised light,

\( \varepsilon \) = concentration of the test solution in mole\(\text{litre}^{-1}\),

\( l \) = optical path of the cell in centimetres.

The following units may also be used to characterise circular dichroism:

Dissymmetry factor:

\[ g = \frac{\Delta \varepsilon}{\varepsilon} \]

\( g \) = molar absorptivity (2.2.25).

Molar ellipticity:

Certain types of instruments display directly the value of ellipticity \( \Theta \), expressed in degrees. When such instruments are used, the molar ellipticity \( [\Theta] \) may be calculated using the following equation:

\[ [\Theta] = \frac{\Theta \times M}{c \times l \times 10} \]

\( [\Theta] \) = molar ellipticity, expressed in degrees\(\text{cm}^2\text{decimole}^{-1}\),

\( \Theta \) = value of ellipticity given by the instrument,
2.2.42. DENSITY OF SOLIDS

The density of solids corresponds to their average mass per unit volume and typically is expressed in grams per cubic centimetre (g/cm³) although the International Unit is the kilogram per cubic meter (1 g/cm³ = 1000 kg/m³).

Unlike gases and liquids whose density depends only on temperature and pressure, the density of a solid particle also depends on its molecular assembly and therefore varies with the crystal structure and degree of crystallinity. When a solid particle is amorphous or partially amorphous, its density may further depend upon the history of preparation and treatment. Therefore, unlike fluids, the densities of two chemically equivalent solids may be different, and this difference reflects a difference in solid-state structure. The density of constituent particles is an important physical characteristic of pharmaceutical powders.

The density of a solid particle can assume different values depending on the method used to measure the volume of the particle. It is useful to distinguish three levels of expression of density:

- **Crystalline density**, which only includes the solid fraction of the material; the crystalline density is also called **true density**;
- **Particle density**, which also includes the volume due to intraparticulate pores,
- **Bulk density** which further includes the interparticulate void volume formed in the powder bed; the bulk density is also called **apparent density**.

**CRYSTAL DENSITY**

The density of solids of a substance is the average mass per unit volume, exclusive of all voids that are not a fundamental part of the molecular packing arrangement. It is an intrinsic property of the substance, and hence should

Linearity of modulation. Dissolve 10.0 mg of (1S)(+)-10-camphorsulphonic acid R in water R and dilute to 10.0 ml with the same solvent. Determine the exact concentration of camphorsulphonic acid in the solution by ultraviolet spectrophotometry (2.2.25), taking the specific absorbance to be 1.49 at 285 nm. Record the circular dichroism spectrum between 185 nm and 340 nm. Measured at the maximum at 290.5 nm, $\Delta \varepsilon$ is +2.2 to +2.5. Measured at the maximum at 192.5 nm, $\Delta \varepsilon$ is −4.3 to −5.

(1S)(+)- or antipodal (1R)(−)-ammonium 10-camphorsulphonate R can also be used.

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